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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

JUNE 1938

TRANSFERS OF WATER AND SOLUTES IN THE BODY

Harvey Lecture, January 20, 1938

JOHN P. PETERS

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PROPERLY KNOWLEDGE of the processes by which water and solutes are transferred in the body begins with the discovery of the circulation of the blood by the great physiological pioneer from whom this society proudly derives its name. This aspect of the subject, however, will receive no attention this evening. The movements of water between the blood stream and the interstitial fluids and the important functions of the lymphatic system will also be neglected, since they have been subjects of recent lectures of Eugene M. Landis[1] and Cecil K. Drinker[2] respectively. I shall confine myself entirely to the discussion of the processes which control the motions of water and solutes between cells and the fluids in which they lie. Even in this connection the effects on these movements of changes in the reactions of the blood and body fluids, which have been so admirably elucidated by Dr. Van Slyke, will receive only scant consideration. Since, as Van Slyke has shown, the effects of pH changes derive from alterations of the osmotic pressure relations between media, they represent only a special case of one

part of the subject of this lecture. History must also largely go by the boards to permit adequate presentation of recent experimental work and its implications. My position here tonight is chiefly that of recorder or reporter of investigations that have been carried out over a period of years in my laboratory by a number of persons whose names will appear as the story unfolds. Relevant material from other sources will be mentioned without any attempt to treat the literature exhaustively.

First I should like to consider certain experiments dealing with the composition of the red blood cell and its behavior in its native extracellular or interstitial fluid, the blood plasma. The red blood cell lends itself to study because it can be isolated for examination and because its metabolic processes are quite slow and can be brought practically to a standstill by moderate chilling. There is much evidence to prove that the contents of the red blood cells have the same osmotic pressure as blood serum and are in osmotic equilibrium with the latter. This means that, in spite of the great differences in their composition, both cells and serum contain the same concentrations of osmotically active chemical components. The differentiation is brought about, apparently, by the fact that the membrane of the cell has a highly selective permeability. It is quite freely permeable to water. If blood is diluted with water this water distributes itself between cells and serum in the same proportion as the water which was originally in these media. The consequence is that the cells swell and, if enough water is added, will ultimately burst. Urea and certain other simple organic compounds also penetrate the cell membrane quite freely. Consequently solutions of urea, although they have a definite osmotic pressure, act exactly like water. Furthermore, urea added to serum does not alter the size or composition of the blood cells. To proteins the cells are quite impermeable, otherwise hemoglobin could escape into the serum. The molecular concentration of protein in the red cells is more than three times as great as that in the plasma. *A priori* it might be expected that the osmotic pressure of the cellular contents would be far greater than that of serum. It is a similar difference in concentration of protein between plasma and interstitial fluids that, according to the Starling theory, balances the hydrostatic force of the blood pressure and retains fluids in the blood stream. In the equilibrium between cells and serum, however, the unequal distribution of protein is compensated by impermeability to other substances, especially the cations, sodium, potassium, calcium and magnesium. If red

blood cells are suspended in solutions of sodium chloride of varying strength it will be found that they retain their original size and shape in that solution which has a concentration of about 0.9 per cent NaCl, or approximately 150 millimolar. Since NaCl in solutions of this strength is almost completely dissociated into Na^+ and Cl^- ions, the solution contains 300 osmotically active milliequivalents. Cells behave in this solution, however, quite differently than they do in a 300 millimolar urea solution. In the latter they swell as they would in so much water. They do not swell in the sodium chloride solution because the sodium is unable to cross the cell membrane. In sodium chloride solutions stronger than 150 millimolar the cells shrink, in weaker solutions they swell. The degree of expansion or contraction depends on the concentration of salt which is added. Equilibrium is reached in each case when enough water has been transferred across the cellular membrane to equalize the concentrations of active osmotic solutes on the two sides of the membrane.

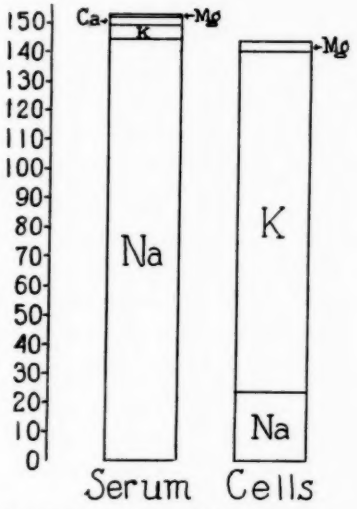

Fig. 1—The average molar concentrations of base in human serum and red blood cells.

After these few preliminary remarks I should like to present certain data and experimental results. Fig. 1 shows the concentration of anions

and cations in normal serum, not as they are usually given, in relation to units of volume, but as osmotic equivalents (millimols) per liter of water. These data are from analyses made by Miss Pauline Hald.[3] The total concentration of base in serum water, 153 millimols, is approximately the same as that of an isotonic salt solution, 150 millimols. For purposes of calculation, then, it should be possible to use the concentration of base in serum as a measure of the effective osmotic pressure of the serum, that is, of the components of serum which cannot cross the cell membrane and which, therefore, will determine the distribution of water between cells and serum. If this is true and if the cell membrane is completely impervious to base, it should follow that, when water or salts or both are added to blood, the concentrations of base in the serum before and after the addition should vary inversely as the volumes of water in the cells.

$$\frac{Bs_1}{Bs_2} \text{ should equal } \frac{Wc_2}{Wc_1}$$

Where B represents mols of base per kilo of water, W kilos of water, the subscripts s and c, serum and cells, and 1 and 2 the bloods before and after treatment, respectively. It will be apparent from the figures in Table I that experimental results conform to expectation with surprising accuracy. In these fourteen experiments, performed by Wakeman, Eisenman and Hald,[4,5] the ratios of base and of cell water are almost identical in the great majority of instances, although water, and the sulfates, carbonates and chlorides of both sodium and potassium were added to blood. Since then similar results have been obtained with phosphates of sodium and potassium. These and other experiments of a like nature can leave no doubt that human red blood cells under the conditions of these experiments are quite impermeable to the bases, sodium, potassium, calcium and magnesium, and that, when the concentrations of base in the serum are changed, the cells give up or take on water in such proportions that the osmotic pressures in the two media always remain identical. Fig. 2, from data of Klinghoffer,[6] shows that solutions of urea (marked by circles) and of glycerol (the triangles) have the same effect as so much water (crosses), proving that these substances enter the cells with perfect freedom. Sucrose is unable to enter the cells; therefore in solutions of this sugar red cells behave as they do in salt solutions.

Glucose presents a rather particular case. It has been demonstrated

TABLE I

Relations of Transfers of Water between Cells and Serum to Changes of Serum Base after Addition to Blood in Vitro of Salts or Water

*Experiment No.**	$\frac{W_{c2}}{W_{c1}}$ (1)	$\frac{B_{s1}}{B_{s2}}$ (2)	(1)/(2)	*Added to blood*
1	0.800	0.798	1.00	24.7 m.eq. NaCl and KCl
4	0.849	0.825	1.03	31.3 " "
5	0.817	0.821	1.00	32.2 " KCl
2	0.928	0.942	0.99	9.2 " Na_2SO_4 and K_2CO_3
3	0.869	0.938	0.93	13.9 " " " "
6	0.906	0.907	1.00	12.9 " Na_2CO_3
7	1.334	1.293	1.03	250 cc. H_2O
8	1.260	1.305	0.97	250 " "
1-*a*	0.934	0.926	1.01	11.5 m.eq. K_2CO_3
2-*a*	0.865	0.757	1.14	35.6 " KCl
3-*a*	0.816	0.779	1.05	35.7 " NaCl
4-*a*	1.189	1.268	0.94	200 cc. H_2O
5-*a*	1.230	1.322	0.93	250 " "
6-*a*	0.871	0.882	0.99	19.7 m.eq. Na_2CO_3
Average	...	...	1.00†	

Experiments 1 to 8 are from Wakeman, Eisenman and Peters;[4] the remainder from Eisenman, Hald and Peters.[5]

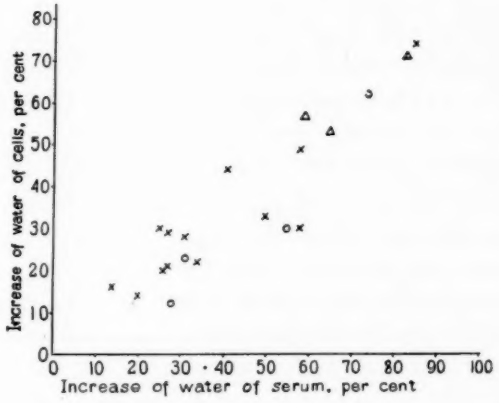

Fig. 2—Per cent increases in water of cells and serum after the addition to blood of water ×, urea solutions o, and glycerol solutions Δ.

repeatedly that in human blood glucose is equally distributed through the water of cells and serum. The addition to blood of dilute solutions of glucose causes cells to swell as they do in water, the glucose and water distributing themselves equally between the two media. In stronger glucose solutions cells do not swell so much, taking up less than their share of glucose. The factors that limit the load of glucose which the cells will assume are not yet clear. Klinghoffer has, however, shown, in some unpublished experiments, that, in spite of this discrepancy in the distribution of the glucose, osmotic equilibrium between cells and serum is still maintained: that is, water and glucose cross the cell membrane in equal proportions, the transfer of water being conditioned by the transfer of glucose. It should be mentioned that the conditions under which glucose is not evenly distributed in human blood are not encountered in life.

With this much established it became necessary to learn whether red blood cells behave in the same manner while they are in circulation in the body. With this end in view Eisenman and Hald[5] examined blood of patients before, and at intervals after, injections of large quantities of hypertonic sodium chloride or sodium sulfate. In these experiments (see Table II) the base of serum increased from 6 to 27 millimols between the two observations, which were made, in two instances, at intervals of as much as eighteen hours. In every experiment except the ones surrounded by the black line, in which a single analysis was probably in error, the ratios of cell water and of serum base agree quite as well as they did in the *in vitro* experiments. It would seem, then, that both in the test tube and in the body the red blood cells respond to changes in the concentration of base in the serum as if they were quite impermeable to base, adjusting osmotic equilibrium by transfers of water alone. As far as their size and water content are concerned, then, these cells would seem to be entirely at the mercy of the serum in which they are bathed.

In early experiments *in vitro*, in which whole blood and serum were investigated by Wakeman and Eisenman[4] it was also proved by direct analysis that no base passed into or out of the cells. This has since been confirmed with more exact techniques by Eisenman and Hald.[5] To our great concern however, when the same techniques were applied to the *in vivo* experiments unmistakable changes in the base of cells were detected. The two series of experiments are contrasted in Table III. The calculated limit of error in the estimation of $Bc_2 - Bc_1$, is 4 millimols, an

TABLE II

Transfers of cell water in relation to changes of serum base.

Experiment	*(1)* $\frac{W_{c2}}{W_{c1}}$	*(2)* $\frac{B_{s1}}{B_{s2}}$	*(1)* / *(2)*
M	89.3	94.7	0.94
T 1-2*	100.0	83.6	1.20
1-3*	96.6	85.9	1.12
2-3	104.7	102.7	1.02
Bo	93.3	96.2	0.97
Be	96.0	97.0	0.97
Cr	93.2	95.8	0.96
Ch	95.3	96.2	0.99
S	94.2	94.8	0.99
Tr	98.7	94.3	1.05
		Average *	0.99

* Experiments T 1-2 and T 1-3 are excluded

TABLE III

Transfers of base between cells and serum

In vivo				*In vitro*			
Exp.	*(1)* B_{c1}	*(2)* B_{c2}	*(2)-(1)*	*Exp.*	*(1)* B_{c1}	*(2)* B_{c2}	*(2)-(1)*
M	97.4	101.3	3.9	1	100.8	101.3	0.5
T 2-3	96.6	87.7	-8.9	2	101.3	105.3	4.0
Bo	98.6	86.3	-12.3	3	117.8	116.7	-1.1
Be	111.7	105.1	-6.6	4	112.3	110.4	-1.9
Cr	101.4	113.5	12.1	5	112.8	113.7	0.9
Ch	107.6	102.2	-5.4				
S	104.9	93.4	-11.5				
Tr	106.6	107.5	0.9				

estimation that seems to be supported by the *in vitro* experiments. Nevertheless this was exceeded in five of the eight *in vivo* experiments, the very experiments in which changes of cell water and analyses of serum gave no evidence of transfer of base. A paradox therefore presented itself.

To find the source of this paradox it is necessary to turn to more direct consideration of the composition of the cells. By reference to Fig. 1 which compares the average molar concentrations of bases per unit of water in serum and cells, it may be seen that there is slightly more total base in serum. In addition the base of serum is overwhelmingly composed of sodium, while in the cells potassium predominates. The concentrations of total base in the two media are, on the whole, sufficiently alike, to

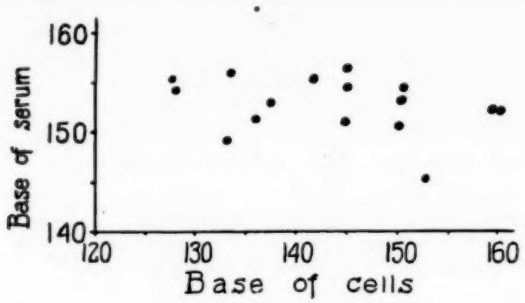

Fig. 3—Comparison of base in water of cells and serum of human blood.

give the impression that, in the cells as in serum, inorganic salts are chiefly responsible for the osmotic pressure. Since the osmotic pressure of both media is the same, the concentrations of base in cells and serum should vary directly. That this is not the case is quite evident from Fig. 3, in which the base of serum is plotted against the base of cells. It is obvious that serum base varies within relatively narrow limits, cell base varies over a much larger range. Furthermore there is no demonstrable relation between the two. At one end of the scale the ratio of cell base to serum base is 0.86, at the other end, 1.05. If these figures are to be accepted potassium and sodium cannot have as important an osmotic role in cells as they do in serum. Osmotic equilibrium can exist when the concentration of base is distinctly higher in the cells than in the serum. In this case, presumably, a fraction of the base in the cells must be osmotically inactive (perhaps because it exists in non-ionized form) or else the serum must contain some unusual unrecognized components. The latter is the less probable explanation, since the composition of serum is simpler and more uniform than that of cells. In those instances where base is far lower in cells than serum, it must be supposed that other chemical substances in cells are bearing more than their usual share of the osmotic load. Regardless of the explanation, unless the analyses are incorrect—and this possibility has been abandoned after exhaustive examination of the methods—it appears that any variation of base in serum is attended by a proportional change of osmotic pressure; whereas the base of cells can vary within wide limits without affecting osmotic pressure.

At first sight this conclusion seems absurd because it is so much at variance with traditional teaching. Emphasis has, in the past, been placed

on the average concentrations of base in cells and serum which, as you saw in the slide a short while back, are nearly the same. Variations in individual bloods were attributed to errors. It was to eliminate this excuse that Miss Hald[7] perfected the techniques by which these analyses were made. On the face of it the results before you are less absurd chemically and biologically than the old concepts. In serum salts make up the major portion of the solutes, and in such a simple medium, may be expected to be quite completely ionized and active. Osmotic comparisons with salt solutions and chemical comparisons with natural and artificial transudates, moreover, have demonstrated that serum meets these expectations. The contents of the cells are far more complex and contain many substances which do not exist in serum, but which must contribute to the osmotic pressure. Moreover, in these cells metabolic processes are causing continuous permutations and combinations of solutes. Complex compounds are breaking down and being again reconstituted in a perpetual cycle. Were there not some mechanism by which these reactions could be, so to speak, osmotically buffered, they would produce constant—sometimes large—changes in volume and water content of the cells. How, if these occur, have they escaped observation? There is adequate precedent for variation of the osmotic activity of base in the combinations of calcium with protein in serum. There must, in addition, be some means by which cells can, in times of need, accumulate stores of material without being forced to take on at the same time excessive amounts of water. The aggregation of glucose into large molecules of glycogen is an example of a reaction that must serve just this purpose. Finally, this cell can not be so utterly impervious to base as our osmotic experiments would indicate or it would be forever deprived of some of the elements that are essential for its vital activities. It remains, then, to discover the mysteries of the facultative permeability of the cell.

In an attempt to learn the significance of the changes of serum phosphate that accompany rapid movements of glucose in the body, it seemed highly advantageous to use whole blood for analyses rather than serum. It had been rather generally assumed that the red blood cell membrane was freely permeable to inorganic phosphate. When Dr. Lena Halpern[8] investigated the subject, this proved not to be the case. The distribution of inorganic phosphate between cells and serum is quite capricious and does not change when potassium and sodium phosphates are added to blood.

And now I should like to make a slight diversion. In all the *in vitro* experiments on permeability that have been mentioned special efforts were made to prevent intracellular activities. Blood was treated anaerobically and kept cool. If exchange of gases is prevented blood can be kept at ordinary refrigerator temperatures for from twelve to twenty-four hours without appreciable change, at room temperature for from two to four hours. If it is warmed to body temperature glucose in the cells is oxidized, organic phosphate esters are broken down to inorganic phosphate and lactic acid is formed. These reactions can be modified by exposure to oxygen or CO_2 and can be reversed by the addition of glucose. Dr. Halpern found that during the glycolytic process inorganic phosphate passed out of the red cells into serum. The process by which it escaped was not merely diffusion, since phosphate was transferred to serum even when its concentration in the latter had been greatly increased by the addition of inorganic phosphate. The escape of phosphate did not denote injury of the cells because the direction of the flow of phosphate could be reversed by the addition of the glucose. It remains only to add that Hald found that potassium accompanied phosphate across the membrane. It can be inferred from these experiments that the red blood cell is always in osmotic equilibrium with its environmental fluid, the blood serum, and responds by changes of volume and exchanges of water to alterations of the concentration of base in serum. As long as it is in the resting state, moreover, its membrane remains impermeable to the bases, to phosphate, to sulfate; but during metabolic activity base and phosphate pass in one direction or another, presumably in accordance with the needs of the cell. These transfers are not accomplished by a mere process of diffusion and must therefore involve chemical reactions.

To demonstrate such exchanges in the body and to measure their osmotic effects has proved more difficult. In the test tube glycolytic processes are accompanied by changes of blood pH, CO_2 and oxygen that confuse the picture greatly. In life it has proved hard to induce transfers of phosphate of sufficient magnitude to cause measurable changes of osmotic pressure. After administration of insulin and glucose, in a few instances, relatively large shifts of phosphate have been demonstrated by Miss Hald and Dr. Margaret Dann.[9] With some reservation it may be stated that these shifts could not be correlated in direction or magnitude with the slight transfers of water which sometimes occurred. This is suggestive, but by no means conclusive, evidence that the phos-

phate and base which were transferred had little or no osmotic activity.

So much time has been wasted on this red blood cell, not because of its intrinsic importance, but because it is peculiarly adapted to such investigations. Throughout it has been recognized that it might prove quite different in its reactions from other more active cells, and therefore a useless model. However, there was continually growing evidence that some of its characteristics were shared by muscle and other tissue cells. These I shall not attempt to treat historically. It has been generally assumed that between the active cells of the body and the blood vessels there is a body of fluid, the interstitial fluid, that has the composition of an ultrafiltrate of serum. Our knowledge of this fluid is entirely based on inference and information obtained in pathological conditions accompanied by transudation. In the latter it must be assumed that the transudates are merely expansions of an already existent body of fluid. If there is interstitial fluid it should have the composition of an ultrafiltrate of serum, being chiefly composed, so far as inorganic elements are concerned, of sodium and chloride. Analyses of muscle tissue by Fenn,[10] the Eggletons,[11] Eichelberger and Hastings[12, 13, 14] and others have proved that the proportions of chloride and sodium in muscle are much the same as those in serum and that the total quantities of these substances in muscle can be accounted for if about 20 per cent of the muscle mass consists of interstitial fluid. Furthermore, if isolated, living, resting muscle is immersed in sodium chloride solutions the salt apparently diffuses into about the same volume of the muscle. Studies by Eggleton[15] indicate that inorganic phosphate, also, diffuses into about the same proportion of the muscle mass. Urea, on the other hand, diffuses freely throughout all the water of the muscle.[16] From these experiments it would appear that there is a barrier to the free diffusion of some solutes through muscle which distinguishes about one fifth of the tissue from the other four fifths. Harrison, Darrow and Yannet[17] analyzed whole animals for chloride, sodium and potassium. They found that, if bone were excluded, the total quantities of sodium and chloride in the bodies of dogs, monkeys and rabbits could be accounted for if 20 to 30 per cent of the body were composed of an ultrafiltrate of serum; leaving enough potassium and magnesium to supply base for the remainder of the water in the body. It seems not unreasonable to believe, therefore, that there is extracellular fluid amounting to about one-fifth of the body weight, and that the remainder of the water in the body, within the cells, is almost, if not quite,

devoid of sodium and chloride. Eichelberger and Hastings[12, 13, 14] have shown that this hypothesis affords an adequate explanation for the changes in the composition of muscle that are produced by injections of normal salt solution, by alkalosis and acidosis and by various dehydrating measures which alter the osmotic pressure of the serum and, therefore, cause the muscle cells to swell or shrink.

To make the analogy to the red blood cell still closer, Pollack, Flock, Mason, Essex and Bollman[18] perfused isolated hind limbs of dogs with blood to which they added inorganic phosphate. Analyses of the muscles showed that the inorganic phosphate did not diffuse into the cells; nevertheless, when glucose and insulin were added to the perfusate the concentration of phosphate esters in the muscles increased. Presumably, then, under the stimulus of metabolic activities chemical processes were activated which conveyed phosphate across a cell membrane which it did not ordinarily traverse. Fenn and Cobb[19] and Thaler[20] have found that potassium can be made to escape from muscle by various measures such as exercise and hemorrhage. Fenn has concluded that the membrane is always permeable to base, but not to anions, and attributes these exchanges to alterations of pH, which have not always been demonstrated.[20] It seems quite as possible that they are expressions of metabolic activities within the cells.

The application of these principles to the analysis of phenomena of human physiology and pathology in a truly quantitative sense begins with Gamble's[21] classical studies of the salt metabolism in fasting and acidosis. Although I shall not dwell on these in detail I cannot refrain from paying him tribute for the inspiration he has given to all those who have worked on problems of salt and water metabolism. Gamble recognized the importance of distinguishing between extracellular and intracellular losses of water and salt and demonstrated the disasters that come from reducing the osmotic pressure of the body fluids by depleting them of salt. He also demonstrated the tenacity with which osmotic pressure is maintained in the face of metabolic disorders. He pointed out the intracellular segregation of potassium and the extracellular distribution of sodium and chloride, and the possibility of distinguishing by balance studies the source of losses of cations and water. It was not, however, possible by the technique which he employed to allocate these cations with accuracy nor to measure directly the relative changes in volume of interstitial and cellular fluids. The chief difficulty in this respect lay in

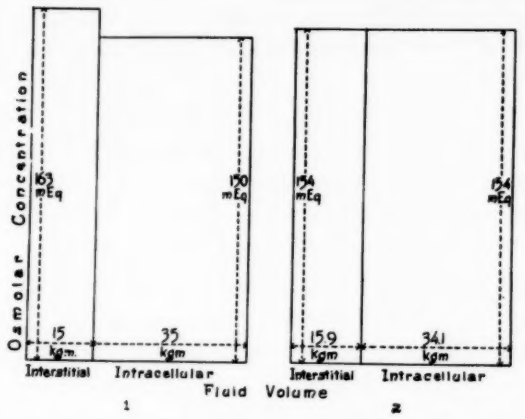

Fig. 4—The effect of adding salt to interstitial fluid.

the fact that, even if sodium is entirely confined to the extracellular fluids, changes in its concentration, because they alter osmotic pressure, will disturb the distribution of water between cells and interstitial fluid. This is illustrated in Fig. 4. In the first part are shown two solutions, each containing base in a concentration of 150 millimols per liter, separated by a membrane which is pervious only to water. If enough salt is added to the smaller compartment to increase the osmolar concentration by 13 millimols, water will enter from the larger compartment until the osmolar concentration is again equalized. At this point, pictured in the second part of the figure, it will be found that, since the ultimate osmolar increment in both compartments is identical, the effect on the concentration of salt in either compartment will be the same as if the salt had diffused freely through the membrane. The volumes of the two compartments have changed; but those changes of volume cannot be detected by the usual methods of chemical examination which measure concentration only.

Theoretically this difficulty could be circumvented by a simple expedient. If, instead of one substance, two substances were used, which originally existed in plasma in different concentrations, it should be possible by simultaneous equations to determine how far they were diluted by water derived from the cells or concentrated by passage of water into the cells. The two substances chosen were sodium and chloride. I shall not tire you now with the details of the experiments which have been published by Lavietes, D'Esopo and Harrison.[22] Suffice it to say

that the concentrations of chloride and sodium did not differ enough to permit accurate deductions from clinically practicable procedures in any but extreme cases. The results were, however, sufficiently compatible with our premises to stimulate new endeavors.

Some method of measuring the interstitial fluids was obviously needed. Substances must be found which were not normal constituents of serum and which would pass freely through vascular walls without penetrating cells. To make a long story short, after searching the literature and considering the adventures with red blood cells, three substances were selected that seemed likely to meet requirements: sulfocyanate, which Crandall and Anderson[23] had shown diffused through about 20 per cent of the body; sulfate and sucrose, neither of which penetrated the red blood cell. All these substances can be quantitatively recovered in the urine, proving that they are not subjected to chemical or metabolic changes. For various reasons none proved quite ideal for the purpose for which it was intended. Sulfocyanate enters red blood cells and apparently combines to some extent with the lipoids of blood plasma; sulfate and sucrose are excreted too rapidly by the normal kidney. In addition sulfate figures must be corrected for endogenous serum sulfate as well as endogenous sulfate excretion. Nevertheless some encouraging measurements were made by Lavietes, Bourdillon and Klinghoffer.[24] The principle of the methods was quite simple. The test material was injected (or, in the case of sulfocyanate, sometimes ingested). After an appropriate interval samples of blood and urine were collected and analyzed for the test substance. The total amount injected minus the quantity excreted, divided by the concentration in the water of serum, will give the volume of fluid in which the material is dissolved if it is distributed through this field in a uniform manner. Results of certain comparisons of the distribution of the three test substances are given in Table IV. When the objections to the three substances are considered, the agreement appears highly satisfactory. It is hard to escape the conviction that there is a barrier which separates the fluids of the body in a broad way into two compartments, of which one, into which these substances chiefly or solely diffuse, makes up roughly 20 to 30 per cent of the body weight, for that is what these figures imply in terms of the total body mass.

An attempt has been made more recently by Purple and Lavietes[25] to utilize the same principle for the measurement of the total water of the body. For this purpose urea, because of its known universal diffusibility,

TABLE IV

The volumes of distribution of sucrose, sulfocyanate and sulfate in the body.

Subject	*Volume of distribution of*		
	Sucrose liters	*CNS liters*	*SO_4 liters*
1	18.8	18.2	
			18.7
	18.3	18.4	
2	18.3	19.0	
3	15.3	17.4	
4		16.6	
			18.8
		17.0	

seemed the most suitable test substance. However, because of the amounts of endogenous urea in the blood and the variability of endogenous urea formation and excretion and the diuretic effect of urea, it proved disappointing. In its place thio-urea was chosen. This compound possesses most of the chemical and physiological properties of urea, and is excreted completely, unchanged, in the urine. It might be considered as a labelled urea molecule. Unfortunately specific quantitative chemical methods for its detection and measurement are not highly sensitive, therefore large quantities of the compound had to be given, so large as to cause serious gastric symptoms. However, before the connection of these symptoms with the drug was established, measurements of total fluids were made on two normal persons and one patient. The volume of distribution varied from 68 to 70 per cent of the body weight, values consistent with accepted conceptions of the water content of the body. Attempts are now being made to refine the analytical technique so that the method may be made clinically feasible.

Meanwhile, since the experiments with sulfocyanate, sucrose and sulfate gave reason to believe that sulfate did not enter cells, it occurred to Bourdillon and Lavietes[26] that the distribution of sodium could be traced more accurately if it were injected in the form of sodium sulfate, earmarking the exogenous sodium ions, so to speak. Large quantities of hypertonic sodium sulfate were, therefore, injected into normal subjects. Blood serum before and after the injections was analyzed for sulfate, chloride, bicarbonate, base or sodium, and protein. In addition oxygen capacity and cell volume of whole blood were measured, and urine was analyzed for potassium, sodium, chloride and sulfate. Finally sodium sul-

TABLE V

Intravenous injection of 102 m.eq. of Na_2SO_4 and 250 cc. H_2O

	1	2	2-1	2/1
Serum SO_4	0.5	15.3	+14.8	
B	148.8	154.5	+5.7	
Cl	98.5	93.1	—5.4	105.8
Distribution volume of				
CNS	16.2	17.1	+0.9	105.5
SO_4	—	12.9		
Change of B estimated from Cl		140.5	+14.0	
Interstitial fluid change from B and SO_4				106.5

focyanate was given in advance of the experiments to serve as a check upon the volume of the interstitial fluid. Time was not given for the sulfate to become completely distributed because this would have permitted the excretion of too much of the salt. The results of one such experiment are shown in Table V. The first column represents conditions before the injection; the second column after the injection; the third column the changes in the blood as the result of the injection; and the last column the ratio of the final volume of the interstitial fluid to the initial volume, estimated by a variety of methods. The quantities of sodium, sulfate and water retained are calculated from the amounts given, corrected for the quantities excreted in the urine. At first sight it might be anticipated that, since equal quantities of the two ions were injected and equal quantities were excreted, the concentrations of base and sulfate in serum would increase to the same extent. Actually sodium rose only 5.7 milliequivalents, while sulfate rose 14.8 milliequivalents. If however, attention is turned to chloride, it is seen that this fell 5.4 milliequivalents, although negligible amounts of chloride appeared in the urine. It would appear, then, that the body of fluid containing chloride was diluted to the extent shown in the last column, 5.8 per cent. Comparison of the sulfocyanate figures indicates that the volume of the interstitial fluid increased from 16.2 to 17.1 liters, a difference of 0.9 liters or 5.5 per cent. If it be assumed that sodium was restricted to the same body of fluid, the sodium originally in this fluid must have been diluted just as much as the chloride. At the end of the injection it should have fallen from its original concentration of 148.8 to 140.5. If this value, which is placed between the first two columns, is subtracted from the final figure 154.5

the actual increment of exogenous sodium is found to be 14.0 milliequivalents, an extremely satisfactory agreement with the 14.8 milliequivalent increment of sulfate. If it be assumed that the increments of base and sulfate were identical it can be estimated from the changes of sulfate and sodium that the interstitial fluids expanded 6.5 per cent. The data are, then, entirely compatible with the theory that sulfate, chloride, sodium and sulfocyanate were distributed over an identical fraction of the total water in the body and that this fraction, approximately one twentieth of the body mass, increased in volume by about 1 liter. If it did expand to this extent some of the extra water must have been acquired from other parts of the body, because the volume added by the infusion, when corrected for that excreted in the urine, amounted to only about 200 cc. The simplest explanation of the facts, in view of other evidence that has been adduced, would seem to be that the sodium sulfate entered only the extracellular fluids. Because it increased the osmotic pressure of these fluids water was withdrawn from the cells to restore osmotic equilibrium. It is possible to calculate that, if this was the case, the cellular fluid volume was about twice as large as the extracellular. This experiment is one of those in which it was earlier shown that the red cells contracted in proportion to the increase of base in the serum, about 4 per cent. The estimated contraction of the tissue cells falls somewhat short of this, which is to be expected since comparison of sulfate and sulfocyanate distributions in column 2 shows that the adjustments occasioned by the injections of salt had not yet come to equilibrium. This is only one of the most complete of a consistent series of experiments by Bourdillon and Lavietes.[26]

In general, then, tissue cells appear to resemble red blood cells in their behavior. There is some evidence that sodium may be more completely excluded from the tissue cells and that these cells are almost, if not quite, devoid of chloride. Furthermore, these two ions are effectively excluded from the cells. When the concentration of sodium in the interstitial fluid changes, osmotic equilibrium is restored by transfers of water to or from the cells without transfers of base. No evidence has been adduced that base is admitted to or discharged from the cells in behalf of osmotic equilibrium *per se*. If these inferences are justified the maintenance of the osmotic integrity of the interstitial fluids should be of prime importance to the function of the cells, which must imbibe water and swell every time the concentration of sodium in the serum falls, or shrivel

whenever it rises. The concentration of sodium in the interstitial fluids controls, however, only the load of water in the cells, that is the dilution of the cellular constituents. The actual quantities of these constituents in the cells—or at least the inorganic components—appear to be controlled by entirely different mechanisms. The impermeability of the resting cell to potassium, phosphate and other chemical substances is an essential protective property. It is equally essential that there be some means to unlock the barrier when need arises in the cells for more of these materials or for the discharge of any excess. Apparently the key to the barrier is entrusted to the metabolic processes of the cells, thus insuring automaticity.

Although potassium is the predominant base of all cells, including the red blood cell, it is quite as impossible to drive potassium as it is to drive sodium across the membrane of the resting red blood cell. This may not be true of other cells. Bourdillon[27] has found that when potassium chloride is given by mouth, the potassium distributes itself through a larger volume of fluid than the chloride does, a volume that approaches the total amount of fluid in the body. It seemed possible that the potassium might be absorbed from the gut more slowly or less completely than the chloride. But, when Winkler (unpublished studies) gave potassium chloride intravenously he obtained similar results. The increments of serum potassium and chloride in these experiments, which were conducted on human subjects, are small; but the differences in the increments are consistent and unmistakably significant. Moreover, in similar experiments Bourdillon found that, after sodium chloride, increments of sodium and chloride were the same. These experiments, if they are substantiated by further work, can only mean that inorganic potassium, when it gains access to the interstitial fluids, passes freely into the cells. Since exogenous potassium is excreted quite rapidly, it must escape from the cells with the same ease. The red blood cell model at this point fails. Of course the potassium which cannot be found in the interstitial fluids may seek other repositories than the cells. To jump to this conclusion at once is quite unjustifiable. It is equally unjustifiable to assume that the mere increase of potassium in the interstitial fluid initiates some metabolic disturbance by which it is conveyed into the cell. Since the volume of distribution of the potassium approaches the total fluid of the body, the simplest hypothesis is that inorganic potassium diffuses freely across the cell membrane. In this case, the intrinsic potassium of cells, since it does not diffuse

outward, must be restrained from free diffusion by some force other than the mere impermeability of the envelope of the cell.

This would not be incompatible with any of the facts thus far presented. So long as sodium is ionized and cannot gain access to the cells, changes of its concentration must control the size and water content of the cells. If inorganic potassium can diffuse freely between cells and interstitial fluid it would have no influence upon the distribution of water. This fraction of potassium is quite small. The great mass of potassium may be relatively non-ionized, combined with organic phosphate esters and protein. Presumably this would be in equilibrium with the moiety of ionized inorganic potassium and, therefore, not entirely unaffected by the concentration of the latter. Its concentration would, however, depend far more upon the material available for the formation of the compounds in which it is found, of which phosphate is presumably one of the most important components. Since phosphate can enter or leave the cell only under the stimulus of metabolic processes, movements of potassium would be conditioned by these same metabolic processes which control phosphate. All this discussion of potassium is, of course, highly speculative in comparison with the preceding discussion of sodium, which is experimentally documented. It is, however, consonant with the physiologic and pathologic data now available.

Gamble[21] found that in the dehydration of starvation acidosis potassium as well as sodium was wasted. This he connected first with losses of protein and glycogen from the cells. Later[28, 29] he discovered that potassium was sacrificed also in the diuresis evoked by acidifying salts, this time without appreciable losses of carbohydrate or protein. It seemed possible that wastage of extracellular sodium might itself provoke the discharge of potassium from the cells and that this might serve to mitigate the effects on the cells of altering the amount of salt in their environment. Nevertheless, in experiments by McCance[30] in which the sodium of the body was greatly depleted by withdrawal of salt from the diet combined with sweating, potassium losses were quite insignificant. In these experiments it was estimated that at least 25 to 30 per cent of the sodium and chloride in the body was withdrawn and the concentrations of these substances in the serum fell 10 to 15 millimols.

In Addison's disease and in some animals after adrenalectomy sodium wastage is accompanied by retention of potassium. This retention, according to the balance studies of Harrop and his associates,[31] causes no

immediate rise of serum potassium. The potassium which is retained apparently enters, or becomes imprisoned in, the cells. Harrison and Darrow,[32] by analyses of the tissues of rats, animals which do not waste sodium, have shown that after adrenalectomy cellular potassium increases without a comparable increase of water. If this is verified, it exemplifies the accumulation in the cells of osmotically inactive potassium. It also suggests that removal of the adrenals gives rise to a widespread derangement of cellular metabolic processes. It has been demonstrated further that adrenalectomized dogs are benefited by restriction of potassium in the diet and can be thrown into shock by the administration of potassium salts.[33] This is consistent with the hypothesis that the intrinsic potassium of the cells is affected by the supply of inorganic potassium in the interstitial fluid. These discoveries of the role of potassium detract in no respect from Loeb's[34,35] discovery that in man and many animals absence of the adrenal cortex causes depletion of sodium and symptoms that can be relieved in whole or in part by administration of sodium salts. Harrison and Darrow's rats, in spite of the fact that they did not waste sodium spontaneously, proved more susceptible than normal rats to withdrawal of sodium. Moreover, when the sodium in their interstitial fluids fell, the tissue cells swelled, proving that they had lost none of their capacity to respond osmotically.

A recent unpublished study by Klinghoffer and Lavietes of a patient with Addison's disease may be reported with a certain amount of reserve. He proved to be on the verge of a crisis and, by the time the three-day study was completed, required cortical extract to revive him. Throughout the whole period of observation, therefore, he was sinking deeper into shock in spite of vigorous administration of saline. From Table VI it can be seen that the concentration of sodium in the serum was only slightly reduced and potassium was normal as were also chloride—and bicarbonate which does not appear in the table. Moreover, because of the vigorous therapy they did not change appreciably. There was a large positive balance of sodium and chloride and a smaller negative balance of potassium. During this period (see Table VII) the volume of the interstitial fluid, measured by sulfocyanate, rose from 20.0 to 24.7 kgm., an increase of 4.7 kgm. Estimations by means of the sodium and chloride balances indicated increases of 3.2 and 3.8 kgm. respectively. The agreement is not perfect, but satisfactory enough under the circumstances. It seems reasonable to believe that the volume of the interstitial fluid in-

TABLE VI

Sodium and potassium balances in a case of Addison's disease.

Composition of serum water

m. eq.	*June 22*	*June 25*	*Change*
Sodium	141.3	140.5	—0.8
Potassium	5.1	4.7	—0.4
Na + K	146.4	145.2	—1.2

m. eq.	*Sodium*	*Chloride*	*Potassium*
Intake	1851	1659	113
Output	1395	1255	227
Balance	456	404	—114

TABLE VII

Changes in distribution of water in a case of Addison's disease

Interstitial fluid

kilos	*June 22*	*June 25*	*change*
from SCN	20.0	24.7	+4.7
from Na	—	—	+3.2
from Cl	—	—	+3.8
Conservative estimate			+3.5
Weight	73.0	74.5	+1.5
Fluid received from cells			+2.0

	m. eq.
Cellular base loss expected	250 to 300
Potassium loss observed	100
Accumulation of cellular K	150 to 200

creased 3 or 4 kgm. At the same time the patient's weight increased only 1.5 kgm. Therefore the interstitial fluid received about 2 kgm. of water from the cells. But with this 2 kgm. of water only about 100 milli-equivalents of potassium were lost, a far smaller amount of potassium than even the most conservative estimates would credit to this quantity of cellular water. This suggests that potassium became more concentrated in the cells. Analyses of blood (Table VIII) showed that the concentrations of potassium and potassium + sodium in the red blood cells were far higher during this crisis than they were a month or two later when

TABLE VIII

Changes in the composition of serum and cells in the blood of a patient with Addison's disease.

Milliequivalents per kilo of water

	June 22	*June* 25	*July* 31	*August* 12
Serum				
Na	141.3	140.5	142.3	143.2
K	5.1	4.7	3.8	5.0
Na + K	146.4	145.2	146.1	148.2
Cell				
Na	20.7	31.2	27.3	15.7
K	142.5	127.2	98.2	107.6
Na + K	163.2	158.4	125.5	123.3

the patient was in excellent condition. Too much emphasis should not be placed upon these quantitations, especially those that deal with the concentrations of base in the red blood cells, because just before the patient died a few days ago in another crisis, the potassium and sodium of his red blood cells had not risen again. However, on this occasion sodium of the serum was distinctly lower. It may be of some significance that in the balance studies water and electrolytes moved in the directions that the experiments of Harrison and Darrow would lead one to anticipate.

In another series of experiments Yannet and Darrow[36] have shown that hyperthermia causes similar osmotically inactive accumulations of potassium in cells; but in this case the changes are restricted to the central nervous system.

Depletion of serum sodium is extremely common in clinical medicine. It is regularly encountered in the states of dehydration which result from severe vomiting, diarrhea or gastro-intestinal fistulae; in diabetic acidosis; in water intoxication; in lobar pneumonia; in terminal stages of nephritis; and sometimes with no discoverable cause. It has been too generally assumed that in all these conditions as well as Addison's disease depletion of base has the same quantitative and qualitative effects. Nevertheless, those who have compared, in any large series of patients, the concentrations of electrolytes in the serum with the physical condition, must have been impressed with the wide range of symptomatology associated with deficits of base and with the variability of the response to restoration of the concentration of salt in the serum. The dramatic condition of the

patient in the crisis of Addison's disease differs strikingly from that of the person who has lost sodium by the vomiting of pyloric stenosis, diarrhea or diabetic acidosis. Mere replacement of sodium and water in a severe crisis of Addison's disease may be little more than a futile gesture; I suspect that the administration of cortical extract in pyloric stenosis or diabetic acidosis would be equally fruitless.

In advanced nephritis the sodium of serum may become greatly reduced. Frequently such salt deficits are attended by disturbances so profound that the condition has been named "uremia from lack of salt". If the advanced nephritic is given a salt poor diet, especially if large amounts of fluid are also administered, both base and chloride of the serum will fall and the weight will usually diminish. Appetite and thirst may fail and the blood non-protein nitrogen often rises even if no more serious symptoms develop. We have reported[37] a nephritic who displayed this tendency to waste sodium to such an extent that when he was given as much as 15 gm. of sodium chloride daily, the chloride of the serum rose only to the upper normal limit, 105 m.eq. When salt was withdrawn it fell gradually to 85 m.eq., at which point the total base of the serum was only 125 m.eq. That is, both sodium and chloride were almost 20 m.eq. below normal, reductions quite as great as those encountered in the crises of Addison's disease. In spite of this extreme salt depletion and the hypotonicity of his serum the patient felt none the worse and exhibited none of the symptoms which commonly accompany such salt deficits. The red blood cells in this case swelled in direct proportion to the reduction of base, and from studies of the electrolyte balance it may be inferred that the tissue cells behaved similarly.[22] Freedom from symptoms cannot be attributed to any peculiar compensatory reaction which protected his tissues from the reduction of osmotic pressure. One peculiar feature was noted: Thirst did not flag when salt was withdrawn and the body weight varied only 2 kgm. in the course of the experiment. He did not suffer the dehydration which usually follows salt restriction in advanced nephritis.

Winkler and Crankshaw[38] have recently reported a series of patients with advanced pulmonary disease, especially tuberculosis, who exhibited a peculiar tendency to waste sodium and chloride in the urine and who had persistently low concentrations of these substances in the serum. The conditions could easily have been confused with Addison's disease except that salt depletion in these cases had no spectacular consequences.

Further examples of the variable effects of salt deficits could be mul-

tiplied to no great advantage. If I should dare to differ from Gamble in any important respect it would be to challenge his statement that the concentration of base in the interstitial fluids is more jealously guarded than is the volume of these fluids.[39] Unfortunately this doctrine is one to which I so long adhered that it ill befits me to do more than confess my own error. Apparently, in this as in other matters, circumstances alter cases and it is incumbent upon us to inquire into the circumstances. The determination of concentrations of salts in the serum is a unidimensional measurement. This must be supplemented by measurements of the volumes of the fluids in which those salts are dissolved if precise information is to be secured about animals which have three-dimensional bodies. Even this does not suffice: the allocation of these fluids and solutes between the various compartments of the body cannot be neglected. Among these compartments the blood stream, the interstitial fluids and the cells must be separately considered. Although the blood serum is only part of the interstitial fluid, the shock of hemorrhage and the edema of heart disease or nephritis can leave no doubt that the distribution of fluid between the subdivisions of this general system is of great moment. Harvey's and Starling's circulations cannot be forgotten. Mere expansion of the interstitial fluid as a whole seems to cause little disturbance; but considerable reduction of its volume, even without change of composition, is not so well tolerated. Changes of its osmotic pressure (i.e., the sodium concentration) usually, but not invariably, provoke serious symptoms. Why there should be exceptions remains to be discovered. Are the untoward effects of base depletion entirely referable to changes in the volumes of the cells as has been suggested? How large a part must be attributed to the concomitant loss of interstitial fluid with which base depletion is usually associated? Do those who apparently escape evil effects escape because the volume of the circulating blood or the interstitial fluid remains relatively unaltered, or by virtue of some compensatory transfer of base or by the inactivation of previously active osmotic components of the cells? Finally, what are the processes that unlock the cellular membranes and possibly alter the osmotic activity of the cellular constituents and how can they be controlled?

It is halting first attempts at dynamic measurements of the distribution of fluids and salts and the forces that govern them which I have tried to describe tonight. Tentative inferences have been drawn of which it is hoped that some at least may survive the acid test of further investigation.

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CANCER OF THE GASTROINTESTINAL CANAL*

The Bulkley Lecture

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VITAL STATISTICS indicate that next to heart disease cancer is the most common cause of death. Constant vigilance to provide earlier diagnosis and treatment is essential if a larger number of patients are to be saved from an untimely death. One of the chief obstacles in the fight against cancer is the pessimism concerning its curability which is so prevalent among laymen as well as a great many members of the medical profession. A knowledge of actual results which are obtainable by good surgery in reasonably early cases will go far in replacing such pessimism by a healthy optimism. Educational campaigns are essential to disseminate known facts. The American Society for the Control of Cancer has set itself the task of educating the general public in the symptomatology of cancer and urging medical consultation. To educate the doctor in properly evaluating early suggestive symptoms and signs is the duty of medical organizations and institutions. Much is being done in this respect, but in spite of this, patients with untreated cancer continue to present themselves with malignant growths in such an advanced state that the tumor is irremovable and any thought of cure has to be abandoned.

In analyzing the reasons for this one may place patients into one of three groups:

(a) Those in whom the cancer comes on so insidiously that no variation from the normal is noticed until it has reached a stage of growth and dissemination which precludes surgical removal. Such cases will always occur and no amount of education can prevent them.

(b) Patients who present a history strongly suggestive of cancer and who give the examiner the very definite impression that if they had consulted a physician at the first appearance of symptoms, their lives might have been saved. This group may gradually be reduced by cancer campaigns.

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(c) In the third group are included those patients who consulted a physician on the first appearance of symptoms or signs, but in whom the importance of these symptoms was not appreciated. A harmless looking or feeling lump may have been dismissed with the remark "just a little gland, as long as it does not hurt, do not bother about it". A discharge may have been treated with a douche without investigating its source. For symptoms of indigestion prolonged medicinal treatment may have been instituted instead of diagnostic tests. An x-ray examination may not even have been considered. It is this group of cases which is put squarely at the door of the doctor. It is our duty and responsibility to educate ourselves so that this group will become steadily smaller. To do so it is necessary to keep the subject constantly before the medical profession. This has been recognized by many and efforts are being made all over the country to help reduce cancer mortality by properly directed educational campaigns.

The late Dr. L. Duncan Bulkley, a distinguished member of this Academy, and a well-known dermatologist, who was intensely interested in cancer, was one of those who recognized the value of postgraduate education in this branch of medicine. He established the Bulkley Lecture at The New York Academy of Medicine in 1929 for the purpose of annually bringing some phase of this vital subject to the attention of the general practitioner.

We can tell you nothing new nor startling for the knowledge concerning cancer has been built up gradually. Many men have contributed to it until today it is manifest that the application of this knowledge saves many lives which were formerly lost.

Cancer of the gastrointestinal tract is a large subject for one lecture. It is realized that the inclusion of the esophagus, stomach, the entire intestines, especially the colon and rectum, makes it impossible to go into great detail. Nevertheless it was thought advisable to present it in this comprehensive way in order to bring out certain pertinent points concerning symptomatology, laboratory findings and treatment which are common to all parts of the canal.

The chief functions of the gastrointestinal tract are the digestion and absorption of food and the elimination of the non-used waste products. An important associated function therefore must be the regular propulsion of its contents through the canal. Any interference with this mechanism leads to disturbances which manifest themselves as

symptoms. These disturbances in turn may initiate other symptoms or physical signs. Carcinoma tends to narrow the lumen of the alimentary canal wherever it happens to develop. This produces interference with the propulsive mechanism, hence symptoms due to some degree of disturbance of the mechanical function are the most likely. This in turn leads to interference with normal secretion, absorption and elimination and initiates a symptom complex of nutritional disturbance which produces weakness and loss of weight.

The entire gastrointestinal canal is about twenty-five to thirty feet in length, of which only nine to ten inches form the esophagus and a similar length the stomach. Of the remainder, four-fifths form the small intestines and one-fifth the colon and rectum.

The lumen of the canal varies a great deal in size and it appears that cancer is most common where it is narrow and offers opportunity for stagnation and irritation. The rarity of cancer of the small intestines is explained on the theory that its fluid contents flow along a fairly uniform lumen without obstruction and irritation. This theory accords with our present day conception of the etiology of cancer, which seems to point to chronic irritation in a susceptible individual as the most likely cause. In all locations of the gastrointestinal tract in which cancer is commonly encountered such factors can usually be adduced.

In the esophagus coarse and poorly masticated food, very hot or other irritating food, may produce cell changes at the physiological narrowings. In the stomach improperly masticated food, changes in secretory activity with spasm, retention and irritation may well play a role. In the colon stagnation with formation of toxins and secondary irritation offer a fertile field for the development of cancer.

Figures concerning the incidence of cancer vary a great deal, depending on the source, whether from clinical medical, surgical or autopsy material. According to the vital statistics of New York City for 1936, cancer of the esophagus constitutes about 3.1 per cent of all cancers, cancer of the stomach 17.2 per cent, cancer of the small intestines 0.2 per cent, cancer of the colon and sigmoid 12.7 per cent and cancer of the rectum and rectosigmoid 7.2 per cent.

The proportion to all cancers of the gastrointestinal tract is about: 6.1 per cent in the esophagus; 33.8 per cent in the stomach; 0.4 per cent in the small intestines; 25.1 per cent in the colon and sigmoid; 14.2 per cent in the rectum and rectosigmoid.

Except in the esophagus and in the anal canal, which are lined with squamous epithelium and usually give rise to epithelioma or epidermoid carcinoma, all cancers of the gastrointestinal canal are adeno-carcinomas. They arise from the columnar epithelium lining the entire tract. Though they have the same origin, there is considerable difference in the gross as well as in the microscopic appearance of these tumors. Some are small, somewhat pedunculated or polypoid, project into the lumen and do not early penetrate into the wall. Others form flat serpiginous ulcers with overhanging edges and have a great tendency to penetrate the gut wall. Still others form large bulky masses or very small scirrhus tumors. Gelatinous or mucoid degeneration may take place and still further complicate the picture. An explanation for this behavior is to be found in the normal difference of cells in the various sections of the alimentary canal, in the virulence of the cancer cells, as well as in the reaction of the host to the invasion of malignant cells.

The difference in development of cancers of the gastrointestinal tract explains some of the differences in their clinical manifestations as well as in their course and prognosis. It is known that the papillary types of tumor which project into the lumen offer a more favorable prognosis than those invading the wall and involving the peritoneal coats, and they are of a lower grade of malignancy. However it is not only the lower grade of malignancy which makes them more favorable, but the fact that they may give rise to bleeding, or if favorably situated, produce intestinal obstruction and thus become recognized before invasion of lymph nodes has taken place. The small scirrhus cancers on the other hand are frequently not recognized until very late. They give rise to no bleeding and the increasing constipation receives scant attention except an increase in the dose of a laxative until acute intestinal obstruction supervenes. Then again large massive tumors may give rise to bleeding or obstruction and in addition to that they may be palpable.

The early symptoms produced by a malignant growth are unfortunately so vague that they are difficult to recognize. If allowed to go untreated, the outstanding symptom common to nearly all cancers of the gastrointestinal tract is obstruction; but as we have just explained, this symptom may appear early or late. Thus a growth developing at a narrow portion of the canal, and projecting into the lumen may produce a mechanical obstruction and lead to recognition early. A similar growth developing in a wide portion of the canal may grow to a large size,

perhaps never lead to obstruction and become recognized chiefly because of its bulk, or because of bleeding, or breaking down with resulting toxemia or anemia.

It is usually some degree of obstruction, vague though it be, which first attracts the patient's attention. Whether this obstruction is in the esophagus, the stomach, or the intestines, spasm is immediately added to the mechanical factor, and congestion with more or less stagnation results. Added to this are secretory changes, disturbed digestion and a whole train of symptoms depending on the location and extent of the lesion.

The diagnosis of early lesions depends to a large degree on the alertness and experience of the examining physician. Does he on the basis of symptoms presented suspect carcinoma? It cannot be stressed too often how important it is not to overlook what appear to be vague or unimportant symptoms such as loss of appetite, indigestion or any change in the bowel habit.

Changes in function due to some narrowing of the lumen are the most important. They may not approach actual obstruction but be sufficiently marked to temporarily delay the passage of food or intestinal contents. Depending on the location one may have discomfort or difficulty with swallowing, fullness in the stomach associated with belching, nausea and occasionally vomiting, anemia due to bleeding, absorption of retained material or products of the tumor, possibly constipation and diarrhea alternating, or difficulty with gas.

Many of these lesions being ulcerative, there may be blood, either in the vomitus or in or on the feces. It may be in small quantity detected only by chemical tests, or it may appear grossly. Chemical tests, especially gastric analysis may be helpful in determining altered secretion, products of stagnation, or blood.

At times one may be able to feel a mass, either in the stomach, colon, or rectum. The presence of a palpable tumor does not mean that it is not removable and should never act as a deterrent to operation.

One may bring a lesion into view with the aid of an esophagoscope, gastroscope or proctoscope.

By far the greatest aid in the detection of lesions of the gastrointestinal tract are roentgen examinations. This is true particularly of those cancers which are inaccessible to palpation or instrumental examination. If done with the proper technique the percentage of error is

slight. Most roentgenologists have developed methods of examination which in their hands rarely fail to demonstrate an existing defect. It has seemed to us that the greatest justification for criticism of procedure in the diagnosis of cancer of the gastrointestinal tract lies in the fact that roentgen examination is not resorted to sufficiently often. With only slight symptoms, even though suggestive, a physician hesitates to subject a patient to the expense involved, and as a result the lesion progresses from a curable one to one less favorable. The important thing to bear in mind and to teach, is to have x-ray examinations made at the first sign of trouble and not to wait until the patient presents a typical picture of advanced disease. To make such examinations more easily possible for everybody may well be the goal of all those interested in Public Health. Any or all of these examinations may be initiated after a good history and physical examination have made one suspect the presence of cancer. One should not rest until the lesion has been found or definitely ruled out. In case that is not possible, careful observation and re-examination at a later date are indicated.

Treatment consists of *destruction* or *removal* of the growth. Destruction is applicable only in readily accessible tumors, and may be carried out by means of radium, Roentgen rays, actual cautery or surgical diathermy. In spite of the fact that some tumors are radiosensitive, radiation therapy has so far not attained the results which had been hoped for. At the present time surgical removal offers the best chance for cure. Only in very favorable cases may one at times carry out local removal with a satisfactory result. Usually radical resection of the tumor with sufficient normal tissue surrounding it, and a portion of gut above and below the lesion, and including the lymphatic drainage area, is the operation of choice.

Cancer of the Esophagus

Owing to the deep situation of the esophagus, and its inaccessibility to ordinary vision or palpation, the older methods of examination were limited, and treatment likewise restricted. Following the advent of the Roentgen rays and the esophagoscope, exact diagnostic methods have been developed, and the successful treatment of carcinoma has advanced considerably.

Cancer of the esophagus may occur at any level, but has certain sites of election which correspond with the physiological narrowings.

The onset is insidious and for this reason medical aid is rarely sought until dysphagia has become manifest. Even then, this symptom is often not given the necessary attention and the disease is allowed to progress until regurgitation of food, salivation, pain and loss of weight occur. All of these symptoms are late manifestations and explain, in part at least, why surgery for cancer of the esophagus has not made more progress.

The chief obstacle to early diagnosis is the vagueness of symptoms. One has to be mentally alert when a patient with slight difficulty during the act of deglutition presents himself. Suspecting a lesion and referring the patient to a competent roentgenologist and endoscopist momentarily ends the physician's responsibility at this point. It is better than to resort to bouginage with its attendant dangers of irritation and possibly perforation. In experienced hands the diagnosis is usually made easily by means of roentgenograms, which in a typical case show an irregular deformity with slight dilatation above it. This should be supplemented by an esophagoscopy and biopsy because errors in diagnosis are possible.

With a definitely established diagnosis the question arises as to what should be done for the patient. It is the aim of treatment to cure the disease, and if that is not possible, to relieve symptoms and prolong life. Radical operation, x-ray and radium treatment, surgical diathermy, bouginage and palliative gastrostomy may be considered. Which course to follow depends on the patient's general condition, as well as on the state of the local disease.

Palliative treatment is used in those patients who refuse radical operation or in whom the disease has progressed beyond the operable stage. Under palliative treatment the following measures may be adopted as indicated:

1. *General Medical Care.* In early cases when swallowing is still possible, a well balanced diet should be arranged, with all food finely divided to prevent stagnation. Attention must be given the heart and kidneys, and bowel elimination aided. Adequate rest is of importance to preserve the patient's strength. In all advanced cases the most important consideration is the administration of adequate quantities of fluids to overcome dehydration and toxemia. One may resort to hypodermoclysis, proctoclysis, or venoclysis. The addition of 5 per cent glucose to any of these is helpful. Whether to tell the patient of the nature of his illness has to be judged in the individual case. Inasmuch as most patients

with this lesion are men, it is frequently advantageous to do so in order to gain their cooperation and to enable them to arrange their affairs. If one has the impression that such knowledge will lead to severe mental depression it may be better to withhold the information.

2. *Gastrostomy*. This should not be reserved as a last resort, but be performed in most cases soon after a diagnosis has been made. Though it is a relatively simple operation which may be done under local anesthesia with a low mortality in patients in fairly good general condition, it is much more dangerous in an emaciated dehydrated individual with poor healing power. Patients frequently object to such an operation because of the annoyance of constantly wearing a tube, and the necessity of having all food administered in that way. To overcome these objections, a Janeway gastrostomy is recommended which does not require the use of a tube except at meal time and which usually does not leak. After it has been in use a short time, and the esophagus has been put at rest, the swelling due to irritation associated with the carcinoma may subside and the patient be able to swallow better than before. In all complete obstructions gastrostomy is a temporary life-saving measure.

3. *Dilatation*. In some clinics this method is used in preference to others. If carefully performed by passing bougies over a previously swallowed silk thread or under guidance of the eye through an esophagoscope, there is probably not much risk connected with it in trained hands. Unless one is an expert, however, perforation with a fatal outcome may result. It gives temporary relief only.

4. *Intubation*. After a carcinomatous stricture is dilated, it is at times possible to insert a tube, which maintains the lumen permanently. These tubes vary in size and are made of rubber or metal. Their introduction requires skillful manipulation and should be attempted only by experts.

5. *Radiation Therapy*. Although classed with the palliative measures it is really intended to be more than that. One's aim is to destroy the tumor either by means of deep roentgen therapy or by the insertion of radium capsules or radon seeds. Unfortunately, such happy results have not been attained so far, but with the modern treatment developed at some clinics, considerable relief and probably prolongation of life may be looked for. Radiation therapy may, of course, advantageously be employed in combination with dilatation, establishment of a gastrostomy or other treatment.

6. *Electrocoagulation.* In selected cases, especially those with an elevated polypoid type of tumor, destruction of the growth may at times be accomplished. One has to be very careful to select only such cases in which the growth is small and superficial, because the destructive action of the coagulation may easily lead to perforation.

Only a small group of carefully selected cases may be considered for radical operation because of the fact that a patient usually has a well advanced carcinoma when he comes under a surgeon's care and because of our present state of knowledge. Because the operation is always a formidable one, the patient should be in fair general condition and one whose symptoms and findings suggest that the lesion is in its early stages.

The surgical approach varies depending on the location of the tumor. The technical problems involved are quite varied and it is therefore best to consider the treatment under the headings of (a) carcinoma of the cervical portion, (b) carcinoma of the thoracic portion, (c) carcinoma of the lower esophagus and the cardia.

Cancer of the upper end of the esophagus is removed from above. At times the larynx and pharynx must be sacrificed because the growth has a tendency to spread into the hypopharynx. For the resulting defect a reconstruction operation may be considered later. A gastrostomy is usually advisable.

Removal of a carcinoma affecting the middle or thoracic portion of the esophagus is technically the most difficult and dangerous. Reports of successful extirpation are increasing in the literature. Ingenious methods of approach have been developed. The best known one, and the one having the largest number of successful results to its credit is the one developed by Torek. It consists of a preliminary gastrostomy, followed by a transpleural resection of the affected esophagus. The upper end is brought out at the neck and is later connected with the gastrostomy by means of a rubber esophagus. In suitable cases a reconstruction of the esophagus may be carried out. The method has lately been modified by dividing the main operation into two stages. Perhaps at the time the gastrostomy is performed, or as an independent procedure, the upper end of the esophagus is brought out at the neck through an incision along the anterior border of the sternocleidomastoid. The tumor is then removed at a later date through the thorax.

Recently there has come a report from England and another from

Germany of the successful extirpation of a carcinomatous esophagus by blunt dissection with the aid of the hands passed through a high epigastric and a neck incision along the entire mediastinum without opening the chest. The lower end is divided, the stumps closed and the entire esophagus drawn out at the neck and removed. Extrapleural resection through the posterior mediastinum has also been successfully performed.

Cancer of the lower end of the esophagus may be removed through the chest or the abdomen. The ideal operation is to reimplant the stump of the esophagus into the fundus of the stomach in order to permit normal deglutition. A gastrostomy is usually not required.

Cancer of the Stomach

According to available statistics, cancer of the stomach is responsible for at least one-third of all male and one-fifth of all female cancer deaths.

The general attitude of the profession regarding carcinoma of the stomach is one of resignation, and is no doubt based on the observation that the majority of patients come under surgical care at a time when resection of the stomach, which offers the only chance of cure, is precluded by the extent of the disease. Even a palliative operation is possible in only a comparatively small group of cases.

With the refinements in diagnosis, with better preoperative and postoperative care, and with meticulous surgery, there has been considerable improvement. Recent statistics by well-known surgeons and clinics offer a distinct note of hopefulness, which encourages one in the belief that general improvement in results may be expected. It should therefore be our aim to have patients with vague gastric symptoms referred early to a physician; to have the physician employ all his resources in making an early diagnosis, and then to have the patient promptly operated on. Even when this has been accomplished, however, a large percentage of patients will still come under observation at a time when the disease has progressed beyond the operable stage. This is due to the fact that cancer of the stomach is frequently so insidious in its onset, and the symptoms so slight that the stomach is not even suspected of being the seat of disease. In the beginning there is often no more than slight deviation from normal health. There may be just a feeling of lassitude, slight loss of appetite and lack of interest. Not until diminution of appetite and a little indigestion appear is there any suggestion

that the stomach may be at fault. As the disease progresses, loss of appetite or a distinct aversion to food, especially meat, becomes more marked; there may be definite discomfort after eating, nausea, belching or eructation. Associated with this may be anemia, loss of weight and occasional vomiting. Inasmuch as indigestion is common in middle life, which may be due to a variety of causes, and is often transitory in character, the patient does not seek medical advice until persistence or severity of symptoms compels him. For the same reasons the physician frequently does not realize the serious implications of comparatively slight symptoms. Instead of subjecting the patient to diagnostic methods which would lead to early recognition of the underlying cause, he is apt to try unduly prolonged medicinal treatment for the relief of symptoms. If we were not dealing with cancer, such a course would not be serious; but the cancer grows steadily while we procrastinate, valuable time is lost and the condition may progress from an operable to a less favorable one. There is no retracing our steps when we have missed an early diagnosis. The battle against cancer of the stomach demands that we think of it whenever a patient presents himself with slight indigestion or aggravation of an old existing indigestion. Thinking of it and feeling the necessity to prove its presence or to rule it out is the only safe guide.

Physical examination is usually negative at the beginning of the disease unless a favorably situated tumor at the pylorus causes early obstruction. In such a case a palpable tumor or a peristaltic wave passing from left to right across the epigastrium point to pyloric obstruction. Usually such findings are an indication of more advanced, but often still operable, disease.

Diagnostic measures which may be employed include a test meal. Many physicians seem to have no faith in its value, but it should still be considered as important supplementary evidence. With its aid one may determine retention and stagnation, changes in acidity and the presence or absence of blood. The significance of all these findings has to be carefully weighed. Retention means obstruction of some kind and requires further investigation. If mechanical in character, cancer is a possibility especially if associated with absence of free hydrochloric acid, the presence of lactic acid and Boas-Oppler bacilli. On the other hand such findings are not pathognomonic of cancer. Normal acidity is not incompatible with the presence of a malignant growth. The presence of blood, likewise is merely an indication of an ulcerative lesion, but not necessarily

cancer. However, given a patient in the cancer age with characteristic symptoms and abnormal gastric findings, the probability of cancer must not be overlooked.

The most important diagnostic aid is a roentgen examination for evidence of a defect, rigidity of the wall, absence of peristalsis, and retention. The technique in experienced hands has developed to such a degree that a positive diagnosis can be made in the great majority of cases. There is no possible excuse for not having an x-ray examination of the stomach made in every patient with vague epigastric symptoms, except perhaps the cost involved. There is no doubt that many more examinations would be made were it not for the financial aspect of it. In the eyes of patients, expenditures like that are always justified with a positive finding; with a negative finding, however, a physician may be called an alarmist and the expense involved is charged against him. Even the affluent often hesitate at the cost of an x-ray examination unless symptoms are severe. Clinic patients of course have all the examinations made which are indicated. The people with small incomes in the great middle class find the cost of a gastrointestinal series beyond their resources. It is therefore frequently dispensed with, though indicated, in the hope that the symptoms may disappear. This point deserves stressing again and again.

If all attempts at diagnosis fail, and suspicion of malignancy persists, an exploratory operation should be considered. It should not be undertaken too lightly, but indications are that it might advantageously be resorted to more often than is the case.

Nothing very positive is known concerning the etiology. In most cases symptoms come on insidiously without any previous gastric disturbance. One is therefore compelled to admit that cancer is probably cancer right in the very beginning in the majority of cases and is not grafted upon a pre-existing disease. On the other hand, it may well develop in the changed mucosa of an old gastritis. The frequent finding of gastritis in connection with cancer lends credence to this theory. If we assume chronic irritation to be the starting point in other parts of the body, the stagnation and irritation due to pylorospasm in association with gastritis may well be an etiological factor. Another possibility is cancerous degeneration of an adenomatous polyp.

The question of the relationship of gastric ulcer and carcinoma is

very interesting and has aroused a great deal of discussion. Some clinics have reported a very high incidence, but the majority of conservative surgeons report between 10 and 20 per cent. There seems little doubt that a certain number of cancers develop on the basis of an old ulcer. In those cases in which ulcer symptoms long preceded the cancer, one may definitely have to assume this etiology. On the other hand the findings of an ulcer with carcinoma does not necessarily mean that the carcinoma has developed on an ulcer basis. Quite the contrary, a carcinoma may ulcerate and sometimes to such a degree as to destroy most of the cancer cells. The question has not yet been solved satisfactorily.

With the present state of our knowledge the treatment of cancer of the stomach is surgical. Experience so far has shown that x-ray treatment is helpful in alleviating symptoms in a small percentage of cases, but it is not curative. Surgery is strongly indicated and is life-saving in many early cases. Surgery is also indicated in more advanced cases; as a matter of fact an exploration should be done in all patients whose general condition warrants it. Though many will be found to be too far advanced, not infrequently one finds conditions more favorable than had been anticipated, and a resection may still be possible. In others a palliative procedure may be done, either a gastroenterostomy alone or combined with exclusion of the pyloric end containing the tumor.

A palpable tumor, even a large one, is no contraindication to operation; it may be found to be readily removable. Any tumor which is removable, is operable. One should not be frightened by the presence of enlarged lymph nodes, but remove them with the specimen. Enlarged lymph nodes do not necessarily mean involvement. They may be inflammatory in character due to absorption from an ulcerating carcinoma.

In a planned operation for cancer of the stomach, which is not an emergency, ample time is available to prepare the patient properly for the procedure. This is one of the most important steps in the handling of the patient, and in connection with improved surgical technique is responsible for the lowered mortality at the present time. Under preoperative treatment may be mentioned attention to the heart, kidneys and lungs in order to build up the patient's resistance. The most important steps, however are the administration of sufficient quantities of fluids by venoclysis or hypodermoclysis to overcome dehydration and toxemia; daily gastric lavage to remove stagnated contents, overcome edema and prevent absorption; oral administration of nutritious fluids which may

still pass through the pylorus; and transfusions to raise the lowered vitality.

Thus prepared, the patient is a far better risk and the surgeon may perform a radical operation which otherwise would seem too hazardous. The operability for cancer of the stomach has been definitely extended by the application of effective preoperative care, so that from 40 to 45 per cent are now operable whereas some years ago, operation was advisable in less than 25 per cent.

The ideal operation consists of the removal of the tumor with a safe margin of normal tissue above and below the lesion and the removal also of the regional lymph nodes along the lesser and greater curvature. Just which technical procedure is used is a matter of the personal preference of each surgeon. The Billroth II method is the one most frequently employed in cancer because of certain advantages over others. Inasmuch as both ends, the duodenum as well as the proximal stomach, are permanently closed, one may make use of the von Petz sewing machine, which is time saving and effectively closes off the ends of the specimen and thereby prevents soiling. It has the further advantage that the gastroenterostomy is placed higher up on the stomach stump which would more certainly provide an open stoma even if a local recurrence should develop.

The postoperative mortality is influenced by many factors. It is no doubt higher with a high operability because if a surgeon takes a chance to extend the benefits of a radical resection to those who would be rejected by others, some increase in mortality rate may be looked for. However in the hands of good surgeons the increased risk may be compensated for by the greater skill. About 20 per cent is perhaps as low as may be expected with a high degree of operability.

The final results are the index of the value of radical operation. Considering untreated carcinoma of the stomach a rapidly fatal disease, it is gratifying to know that with an operability of 40 to 45 per cent a five year result of 30 per cent or more may be looked for. The following table published by Balfour is an indication of the progress which has been made.

Our own results, though covering only a small series of cases, correspond rather closely to those of Balfour. We have extended operability to include very difficult cases which would probably have been rejected by many surgeons for a radical procedure. From the results one may gain some encouragement in continuing the fight. Improvement is to be looked

TABLE I

Operative Experience in Carcinomata of the Stomach (Balfour)

Procedure	*Number of Cases*	*Percentage*
Resections	2,112	45%
Gastroenterostomy	815	17%
Exploration	1,866	38%
Total	4,793	100%
Five Year Results		
With lymph node involvement		18%
Without lymph node involvement		48%

TABLE II

Operative Experience in Carcinomata of the Stomach (Eggers)

	Number	*Percentage*
Total Number of Cases	63	100 %
Resections	28	44.4%
Postoperative mortality	5	17.9%
Total resections of five years' standing	18	
Lymph node involvement present in	12	
Survivors in five-year-resection series	6	
Five-year survivors in which lymph node involvement was present	1	

for in earlier diagnosis, proper preoperative care of the patient, and good surgery.

CANCER OF THE COLON

Under this heading are presented malignancies of the cecum, ascending, transverse and descending colon, as well as those of the sigmoid. The reason they are classed in a group by themselves, in distinction from those of the rectum and rectosigmoid, is that there is a marked difference in the therapeutic problems involved. In the former group it is usually possible after resection of the affected portion to reestablish continuity of the gut with subsequent normal bowel function. In the latter group on the other hand a permanent artificial anus is the usual price the patient has to pay for a cure or attempted cure.

Cancer is much more common on the left than on the right side of the colon, the proportion being about two to one. The most common site is the sigmoid. It is well known that cancer has a tendency to develop where anatomically the gut is the narrowest. Surgeons and pathologists have speculated on the underlying reasons for this and it seems probable that the difference in the lumen with the added opportunity for stagnation and irritation play a rôle. Added to this one may consider

that the more solid constituents of the colon on the left side and the great accumulation of toxic products are factors. Of late years the frequent occurrence of polypi of the sigmoid and rectum with malignant degeneration has attracted considerable attention. Experience has further shown that usually tumors of the right side of the colon are less dangerous than those of the left, with respect to infection, as well as to the tendency to metastatic invasion of lymph nodes and the liver. It is interesting to observe that pathologically there is frequently quite a difference in the type of tumor encountered. On the right side they are usually flat, or ulcer like, or large bulky masses; while sigmoid tumors are frequently small scirrhus growths which encircle the gut.

These various considerations to a large degree explain the difference in symptomatology, and provide a reasonable explanation for the fact that most patients come under observation only many months after the first manifestation of symptoms. A tumor developing in the large cecum for instance, does not interfere with bowel function, it does not bleed until it ulcerates and it may not produce a palpable tumor. It therefore escapes attention until a massive tumor either becomes palpable and begins to obstruct the flow of intestinal contents, or by ulceration and absorption of breaking down tumor tissue, produces toxemia, bleeding and anemia. A similar tumor at a narrow portion of gut, such as the hepatic or splenic flexure may produce narrowing of the lumen early and thereby lead to recognition. In the sigmoid on the other hand, an encircling scirrhus tumor which grows slowly, may not lead to striking symptoms until actual obstruction suddenly appears. The symptomatology depends chiefly on the interference with the flow of intestinal contents. Obstruction at some time in the course of the disease is the chief symptom. It is usually chronic, but not infrequently acute obstruction supervenes, especially in the sigmoid. In any middle aged or elderly person with obstruction, if strangulated hernia or bands of adhesions can be ruled out, carcinoma of the colon is the most rational diagnosis.

The obstruction is usually slow and progressive which permits the gut to accommodate itself to the changed condition by hypertrophy of the bowel wall and by rendering fluid the intestinal contents above the obstruction in order to permit passage through the narrowed portion. The resulting changes in bowel habit, consisting of either increasing constipation, or attacks of diarrhea, or alternation of these symptoms, may early draw attention to the real underlying cause. If a temporary

acute obstruction supervenes which so frequently happens when a hard particle of feces or a foreign body becomes lodged in the stenosed gut, investigation is urgently called for. While these changes gradually take place in the gut, the general health suffers due to dehydration and toxemia, and a progressive loss of weight and strength results. At times there is marked anemia especially with the large bulky tumors. Ulceration usually takes place in the tumor with consequent toxic absorption and bleeding. Examination of the feces therefore frequently results in the finding of blood. It may be occult if coming from a lesion higher up in the colon, or bright red, accompanying defecation or clinging to the fecal masses, if arising from a tumor situated in the lower colon.

Patients not infrequently complain of pain, usually cramp-like in character and associated with the retention of gas. They often feel gas "stick" in a certain place and possibly always in the same place, which is a symptom requiring investigation. They may feel and hear gurgling in the intestines and have general discomfort. At times they have explosive movements. All of these symptoms are important if appearing in a patient who has formerly not suffered in this way, and they call for investigation. On examination one may find nothing abnormal, especially not if the abdomen is distended. Many elderly people habitually have a distended abdomen and in that case it is of no value as a diagnostic sign. However, if it has appeared but recently this distention in itself may be an important sign. One may be able to elicit tenderness, particularly over a distended loop proximal to a growth, and one may be fortunate enough to detect peristalsis. This, however, is usually present only in an advanced case with threatening obstruction. At times a tumor mass is palpable. The examiner may discover this accidentally during a routine manual examination or his attention may be drawn to it by local symptoms. Tumors of the cecum, sigmoid and other parts of the colon may thus be palpated but those of the hepatic and splenic flexures are frequently hidden.

Most important in the diagnosis is an x-ray. Experience has shown that a barium meal when it hardens in the intestines is liable to block a stenosed lumen of gut and thereby precipitate an acute obstruction. Physicians have therefore largely abandoned this method of examination as a routine in all suspected malignancies of the colon, and are resorting to a barium clysma instead. It is safer; the findings are known more promptly and the results of examination are generally more satis-

factory. With proper preparation of the colon in a suspected case the demonstration of a defect in the lumen is usually not difficult. However, overlapping of a tumor by a loop of gut filled with barium has frequently led to errors in diagnosis, especially so with a redundant sigmoid. In order to avoid such errors roentgenologists have developed a special technique for colon lesions. A prerequisite is a clean colon, best obtained with the aid of an enema or irrigation. The contrast mixture is then allowed to run in slowly under guidance of the fluoroscopic screen. Abnormalities are noted and plates are then made in different positions. One of the most important is the oblique which permits unfolding of the entire sigmoid with the aid of a certain amount of pressure. After defecation additional plates should be made. Lately a special technique which makes a study of the mucosal pattern possible, has been added to the diagnostic resources of the roentgenologist. In cases of acute obstruction also, the x-ray has a certain value. An ordinary flat plate may show distended loops of gut containing air, or there may be fluid levels in the lumen. A carefully administered barium clysma may show the site of obstruction and thereby aid in the selection of the indicated operative procedure.

The treatment depends on the location of the lesion, as well as on the state of the disease. In acute obstruction one has different problems to consider than in chronic incomplete obstruction or in early cases. The immediate indication in acute conditions is relief of the obstruction, usually by means of a cecostomy or a colostomy. A preliminary x-ray may help in choosing the proper site for the incision. The question of coping with the tumor comes up for consideration after the acute symptoms have subsided.

In all early cases and in those with chronic incomplete obstruction a planned operative procedure is possible. This should be preceded by a period of preparation to allow local inflammatory conditions to subside and to build up the general resistance of the patient. Especially if there have been attacks of obstruction the gut wall is edematous and infiltrated and there may be a certain amount of pericolonic inflammation. Daily enemas or laxatives, combined with bed rest, will help to restore tissues to a condition which permits handling with less danger of spreading infection. If it cannot be accomplished in this way a preliminary cecostomy or colostomy is indicated. In the meantime measures are undertaken to increase the patient's general resistance. This is done by

the administration of nutritious fluids by mouth, or by venoclysis and hypodermoclysis. Transfusions are of great value and should be resorted to freely.

The operative procedure itself varies with the location of the tumor. In lesions affecting the ileocecal junction, the cecum, ascending colon and hepatic flexure, a resection of the right side of the colon with subsequent ileocolostomy is the operation of choice. In suitable cases the entire procedure may be carried out in one stage. In case the patient's general condition is not favorable, or if there have been obstructive signs, it is best to divide the operation into two stages. The first step consists of doing an ileocolostomy by uniting the distal end of the ileum with the transverse colon. It usually results in prompt improvement in the patient's condition which will permit the second stage to be performed after a few weeks. The abdomen is opened through the same incision and the entire right colon with the stump of the ileum and all lymph nodes, removed in one mass.

Tumors of the transverse colon, the splenic flexure or the descending colon are best handled by resection and subsequent end to end or lateral anastomosis. It may be done in one or two stages as indicated. A certain amount of mobilization of the gut is usually required to permit suture without tension.

The most important tumors of the colon, from the standpoint of frequency, therapeutic problems involved, and danger, are those of the sigmoid. Unfortunately a large percentage of patients with carcinoma of the sigmoid are admitted with symptoms of acute obstruction, while others are so far advanced that complete removal is not possible. The most ideal are naturally those without lymph node involvement. Prognosis in those patients is very good, though sometimes there are early metastases to the liver.

The Mickulicz operation is commonly employed. It is efficient when no nodes are involved and the sigmoid is long and has a wide mobile mesentery, so that one may simply bring out a loop of gut with the tumor without interfering with its blood supply. However, if the tumor is large and fixed, the mesentery short and lymph nodes involved, the operation has serious shortcomings. If one attempts to get beyond the nodes at the first stage, one may interfere with the blood supply and cause gangrene beyond the exteriorized loop, resulting in leakage and peritonitis. It has the additional disadvantage in such cases of making it

practically impossible at the second stage to get beyond the nodes because of matting together of the tissues. One, therefore, may have to be satisfied with an incomplete operation. For these reasons different methods of procedure have been advised. One may at times perform a primary resection, and in our hands this has given very good results in properly selected cases. In other cases one may effect either a cecostomy or a colostomy proximal to the tumor for decompression of the bowel, and later follow with a resection of the tumor and anastomosis of the gut. Rankin is a strong advocate of what he calls obstructive resection of the gut, after preliminary decompression.

Whatever method one chooses, it is important to resect the tumor together with the lymph nodes draining the affected portion of gut. It is a safe procedure after edema and infection have been overcome by draining and irrigating the bowel. Rankin with his extensive experience has some very illuminating statistics concerning five year results. He further demonstrates that the intrinsic activity of the cancer cell as measured by Broder's classification of malignancy plays an important rôle in these results. He points out that most cancers of the colon fall into the lower grades where metastases are slower, lymph node and hepatic involvement correspondingly lower, and in consequence, the result more favorable following successful removal.

TABLE III

Operative Results in Cancer of the Left Colon (Rankin)

	Grade 1	*Grade 2*	*Grade 3*	*Grade 4*
Incidence	13%	67%	16%	4%
Five year cures	63%	51%	30%	18%

Our own experience with carcinoma of the sigmoid prior to five years ago is limited to twenty-one cases.

Five patients, or 31.2 per cent, are living over five years, as follows: thirteen, ten, nine, eight and six years. Two of these five, or 40 per cent, had lymph node involvement.

TABLE IV

Operative Experience with Carcinoma of the Sigmoid (Eggers)

	Number	*Percentage*
Total cases	21	
Inoperable	5	23.7%
Operable	16	76.3%
Five year survivors	5*	31.2%

* Two of these five, or 40 per cent, had lymph node involvement.

Cancer of the Rectum and Rectosigmoid

Cancer of this region presents diagnostic and therapeutic problems quite different from those of the colon. While the lesions originating in the rectum may reach a considerable size before symptoms manifest themselves, those beginning higher up, at the rectosigmoid junction, may give rise to obstruction early. Blood in the stool or clinging to the outside of the stool is a common finding, and should insure a most careful examination with the finger and proctoscope. Too often such bleeding is attributed to the presence of hemorrhoids, and not infrequently operation for this condition has been undertaken only to find later that a carcinoma was the underlying cause. Associated with blood in the stool there may be a feeling of discomfort and pressure, as well as a change in the bowel habit, consisting of increasing constipation, perhaps alternating with diarrhea. At times the patients mention explosive movements of gas and thin feces which are due to the collection of fluid intestinal contents above the obstruction until the pressure reaches such a point that they are forced through. Tenesmus and pain may be present, but are often an indication of a more advanced lesion which has become fixed and exerts pressure. Blood in the stool, associated with change in the bowel habit, and fullness or pressure in the rectum should always call for careful investigation. A digital examination must never be neglected, and reveals the size and exact position of any tumor situated in the lower colon. Even the higher lesions can usually be palpated. One may have the patient return for a re-examination after the bowels have been prepared with a cleansing enema. With the patient lying on the side, or in the knee chest position, or in a squatting position, the examining finger can usually reach the growth when the patient is told to bear down. A biopsy may at times be performed without difficulty, but if the tumor is not readily accessible, it should be deferred until after admission to a hospital. In case the suspected growth is not palpable a proctoscopic examination should be done and will usually show a growth within that portion of gut under consideration. Should the examination be negative a barium clysma is indicated, using the technique described under sigmoid lesions.

Theoretically considered carcinoma of the lower segments of the bowel should be diagnosed early because of their symptoms and easy accessibility. Unfortunately that is not the case. For those tumors sit-

uated at the rectosigmoid junction an alibi may sometimes be advanced, in that the tumor has an unfortunate location for diagnosis. It is just too low to be palpable from above and too high to be felt from below. The x-ray may be negative because of an overlapping loop. The employment of oblique x-rays and the more frequent use of the proctoscope should overcome these difficulties. For failure to diagnose tumors situated low, no alibi exists.

In contemplating treatment one has to consider what one wants to accomplish, namely extirpation of the growth together with the lymph nodes draining that area. This latter is essential because almost half of the patients have lymph node involvement at the time they come under observation. To do a palliative operation would be to exclude all these from any consideration of attempted cure. Radium is advocated by some radiologists for tumors situated low, and good results are claimed. Nevertheless the curative value of radium is not well established and is limited to the primary tumor. Electrocoagulation which has recently been mentioned as a method of treatment probably also has a limited usefulness in readily accessible tumors. Great care is required to prevent perforation into an organ or into the peritoneum. Good results have been reported and it may be well to keep it in mind as a method of treatment in selected cases. The greatest objection to it as an attempt at cure is the fact that the lymph nodes are not removed. It would therefore seem to have its greatest field of usefulness in tumors which have remained localized, and as a palliative measure.

Radical operative removal offers the best chance for cure. Several methods of approach and their modifications are available. Surgeons differ somewhat concerning the best method of procedure, whether to attack by the perineal route with or without a preliminary colostomy, or to perform a radical abdominoperineal resection in one or two stages. Less extensive procedures, such as local excision or resection of the rectum with preservation of the sphincter, find application only rarely in well selected cases. There is no doubt that in tumors situated low, a perineal operation may be carried out with sufficient mobilization of the gut to permit resection of the tumor bearing area and suture of the stump to the skin, leaving the new anus in its normal position, without the necessity of a colostomy. There is of course no sphincteric action, but a certain amount of control develops eventually with the aid of the levator muscles and contraction of the opening. Even growths situated

higher may be safely removed from below after a preliminary colostomy which remains permanently. From the standpoint of cancer surgery, however, which aims to remove the primary tumor together with the lymphatic drainage area, there is no question that the abdominoperineal operation is the preferable one. It is readily understandable, therefore, that at the present time surgeons generally are leaning towards the latter procedure.

One of the most important steps in the successful treatment of cancer of the rectum and rectosigmoid is preoperative care consisting of decompression of the bowel, administration of fluids, transfusion, attention to the heart and kidneys. Operation should be delayed until the patient has been rehabilitated, especially if obstructive symptoms have been present. In such a case division of the abdominoperineal operation into two stages, the first one consisting of a colostomy, is advisable.

With proper preoperative care the operability may be extended, operative mortality reduced and good permanent results obtained. In order to judge reported results one has to know the percentage of operability, as it is easy to have a high percentage of five year results with carefully selected cases.

TABLE V

Carcinoma of Rectum and Rectosigmoid (Eggers)

Total Cases	24
Inoperable	8 or 33.3%
Operable	16 or 66.6%
Mortality	2 or 12.5%
Five Year survivors	5 or 31.2%
Still Living (Six, seven, ten and thirteen years)	4 or 25 %

With an operability of 66.6 per cent and a mortality of 12.5 per cent, we have survivors of five years; and longer, of 31.2 per cent.

Rankin, with an operability of 76 per cent has 34 per cent five year survivors.

TABLE VI

Carcinoma of Rectum and Rectosigmoid (Rankin)

Total Cases	300
Operability	76%
Five Year Survivors	34%

Rankin reports Miles with an operability of 30 per cent and 79 per cent five year survivors, while Jones with a higher operability had 50 per cent five year cures.

Such results can be obtained only in carefully selected cases. With the types of patients presenting themselves to us we feel that we cannot refuse to operate upon all but 30 per cent, and our operability has therefore been extended to include more than twice that number. To obtain good results in such cases should be our aim, and we feel that it is possible by proper preoperative care, and selection of that type of operation which the patient is able to stand and which gives greatest promise of restoration to health. We believe that in tumors situated at a high level, an abdominoperineal operation, performed in one or two stages, has definite advantages because it offers better control of the blood supply, and is therefore less shocking than a perineal operation. In addition to that it gives greater assurance of going well beyond the growth as well as including the involved lymph nodes.

The problems in treatment are well understood and have been largely mastered. The greatest need at present is early diagnosis. The thoughts we would like to leave with you are that cancer in its early stages is curable; cancer in a more advanced stage may still be curable; and that every patient with a positive diagnosis of carcinoma of the gastrointestinal tract is entitled to an exploratory operation, if his general condition permits.

CLINICAL ASPECTS OF HYPERTENSION INCLUDING MALIGNANT HYPERTENSION

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NORMAL BLOOD PRESSURE

An exposition of the clinical aspects of hypertension must have as its starting point a conception of normal blood pressure. Normal blood pressure may be defined as the arterial blood pressure which is sufficient to cause the blood to flow and to deliver a pressure of thirty to forty millimeters of mercury (the pressure necessary to accomplish metabolic exchange) in the proximal part of the capillaries. When the heart and the arteries are intact, and not affected by the degenerative processes of aging, this arterial pressure is about 100 systolic and seventy diastolic, the accepted normal pressure for a child of ten (Judson and Nicholson;[1] Hunter[2]). Any blood pressure above this level is hypertension. The persistence of a youthful blood pressure in adult life is indicative of an absence of arteriosclerotic processes and is not necessarily a hypotensive state as is so often assumed.

AVERAGE NORMAL BLOOD PRESSURE

Advancing years are, as a rule, accompanied by an elevation of blood pressure. The systolic pressure increases more than the diastolic and, consequently, the pulse pressure rises. According to Hunter's well-known table, between the tenth and sixtieth year, the systolic pressure increases thirty-two millimeters of mercury, the diastolic nineteen, and the pulse pressure thirteen. The routine explanation offered for these changes is that through arteriosclerotic processes, natural with aging, the arteries lose their elasticity and become more rigid. These qualities may be measured according to pulse velocities which are found to increase considerably in both the elastic and the muscular arteries (Hallock[3]—Chart 1).

A rigidity of the arterial wall due solely to arteriosclerosis would result in a rise of the systolic pressure, but not of the diastolic; the latter

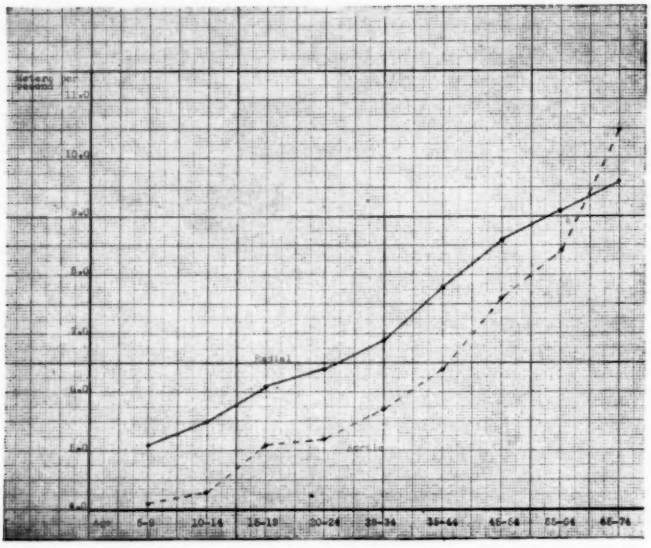

CHART I

Wave Velocities in Elastic and Muscular Arteries at Various Ages

Mean wave velocities (meters per second) in the aorta (elastic artery) and radial artery (muscular artery) at various ages, according to Hallock, *Arch. Int. Med.* 1934, *54 :* 770. Both aortic and radial velocity increase with age. After 55, aortic velocity increases more rapidly than radial; these facts point to a difference between the processes producing rigidity (or loss of elasticity) in the elastic and muscular arteries (arteriosclerosis of elastic and muscular arteries and the degree of muscular tone in the muscular arteries must be considered).

should under such circumstances diminish rather than increase. The fact that the diastolic pressure goes up shows that another element in blood pressure production besides the purely mechanical development of arterial rigidity is involved. It is suggested that the rise in diastolic pressure in the older age periods is due to an augmented tonicity of the muscular arteries. Such a compensatory elevation of tone in the musculature of the larger arteries appears to be the only explanation for the rise in diastolic pressure; it would also account for the increase of pulse velocity in the muscular arteries. A controlled diminution of elasticity of this sort would give the clue to the reason for the almost exact parallelism between the rising pulse velocity and diminution of arterial elasticity with age in the elastic and in the muscular arteries (Chart 1).

Marked Senile Arteriosclerosis and Blood Pressure

The steady progress of arteriosclerosis in the elastic arteries has been mentioned in the previous section. At sixty years, according to Aschoff,[4] the aorta is practically devoid of elasticity. Decrescent changes in the muscular arteries are characterized by calcification of the media—the type of arterial involvement known as Moenkeberg's sclerosis. In many instances although the calcinosis of the blood vessels may be palpated and demonstrated by x-ray, there are no corresponding changes in the blood pressure. This has been attributed by Haynes, Ellis and Weiss[5] to the patchy occurrence of medial calcification—certain areas of the arterial wall being left intact to control the blood pressure. When the entire arterial system becomes sclerotic and rigid it is believed that the systolic pressure becomes very high, the diastolic very low, and the pulse pressure correspondingly large (Bowes;[6] Thompson and Todd[7]).

Increased Systolic Output and Blood Pressure

A rise in pulse volume results in an elevated systolic and a comparatively low diastolic pressure. This occurs with a slow heart rate, especially in heart block; with hyperthyroidism (Read[8]) and with aortic insufficiency. In heart block (Ellis and Weiss;[9] Ellis[10]) and in hyperthyroidism various factors may compensate for the tendency to hypertension and the blood pressure may be normal in spite of an increased systolic output. The spread between the systolic and diastolic pressure in aortic insufficiency depends largely upon the degree of valve leakage. The pulse pressure may be very high, but in some cases it is approximately normal. Aortic insufficiency should be suspected whenever the pulse pressure is as great as sixty millimeters of mercury.

High Systolic, Low Diastolic Pressure of Middle Age

This type of blood pressure is often found, especially in women after the menopause (Saller,[11] Riesman[12]). Calcinosis of the muscular arteries is absent and, consequently, the comparatively low diastolic pressure can not be explained upon the basis of diffuse rigidity throughout the arterial tree. It may be that in such cases there is a lack of compensatory rise in tonicity of the muscular arteries which has been cited in explanation of the elevation of the diastolic pressure in the average normal blood pressure. The frequent occurrence of high systolic pressure and low diastolic pressure, without demonstrable pathological lesions of any sort, should be

recognized. The prognosis of this type of hypertensive disease is much better than when the diastolic pressure is also elevated, and a sharp distinction should be made in the treatment accorded these two varieties of hypertension.

Diet and Blood Pressure

Proteins. The contention that protein foods do not bring about a rise in blood pressure (Mosenthal[13]) has proved to be correct. There is one exception to this statement which may or may not be of clinical significance. Chanutin and Ludewig[14] found that all rats from whom eighty to ninety per cent of the total renal tissue had been removed (corresponding to uremia or a preuremic condition in man) showed hypertension, and that the degree of blood pressure elevation was directly proportional to the amount of protein fed. On the other hand I have found that in human beings with renal insufficiency the blood pressure remains unchanged when the blood urea and the non-protein nitrogen rise or fall markedly in response to dietary regulation.

Carbohydrates and fats. There is no reason to believe that carbohydrates or fats have any influence upon blood pressure except in so far as they may cause obesity. Overweight, contrary to former impressions, does not result in hypertension, but it should be avoided because it places an additional strain upon the heart and arteries. A high blood sugar, whether of short duration or persistent, does not give rise to hypertension (Mosenthal[15]).

Fluids. Since transfusions of as much as 1000 cc., even when given rapidly, do not affect the blood pressure (Mosenthal and Ashe[16]), it is not surprising that the ingestion of large amounts of fluid do not raise the blood pressure (Orr and Innes[17]). The fluid intake should be restricted in the presence of cardiac weakness or edema.

Alcohol. In moderation, alcohol does not influence blood pressure; the hypertension of habitual, heavy drinkers is, in some instances, lowered when the alcohol is restricted or total abstinence is practiced.

Blood Volume and Blood Pressure

One of the assumed causes for hypertension has been, and is, a large blood volume. I remember Theodore Janeway's disappointment when Keith, Rowntree and Geraghty[18] failed to demonstrate an increased blood volume in hypertensive cases. This finding does not eliminate

an augmentation of the blood mass as being a possible factor in elevating arterial pressure. Polycythemia vera is usually cited as a condition in which this occurs, though in this disease the increased blood viscosity must also be considered (Brown and Griffin[19]).

The blood pressure, even when marked hypertension exists, does not rise, but remains unchanged under the stress of rapid transfusions of 1000 cc. of blood (Mosenthal and Ashe[16]). This shows that the body possesses excellent powers of regulating the arterial pressure in the face of enormous variations in blood volume.

The key to the situation probably lies in the fact that the arterial, pulmonary, capillary and venous regions have different functions in regard to the storage of blood. In the capillaries and veins a rise in blood volume should be harbored without difficulty while the quantity of blood remains constant in the arterial system.

Data published by Plesch[20] show that the arteries of the greater circulation contain approximately 250 cc. of blood (Table 1), that is, about the full capacity of the ordinary water tumbler. This is very surprising to most of us but it seems plausible when the matter is analyzed according to the table.

TABLE I

Distribution of blood in the circulation according to Plesch. Note the small volume in the arteries and the large volume in the capillaries and veins, indicating the possibility of their accommodating large fluctuations in the blood mass without disturbing blood pressure or the circulatory flow.

		Blood Volume cc.	
SYSTEMIC CIRCULATION	Arteries	250	2500
	Capillaries	1310	
	Veins	750	
	Left Heart	190	
PULMONARY CIRCULATION	Arteries	125	2000
	Capillaries	1310	
	Veins	375	
	Right Heart	190	
	TOTAL		4500

When we realize that the quantity of blood contained in the arterial system, that is, between the aortic valves and the arterioles, can be measured in a tumbler, and is only a small fraction of the gallon or more which constitutes the total blood volume, it becomes easier to understand the great effect upon arterial pressure of what at first thought appear to be comparatively small changes in systolic output, arterial elasticity,

the tone of the muscular arteries and the contraction or dilatation of the arterioles. The maintenance of a more or less constant blood pressure while the heart and arteries are anatomically and functionally intact, and the extreme lability of blood pressure when the compensatory mechanism is impaired, become less of a mystery when we consider that the arterial blood volume is only a small part of the total blood volume.

Hypertensive Disease

All the varieties of hypertension mentioned thus far are characterized by an absence of rise, or a comparatively slight rise of the diastolic pressure. Hypertension, when it becomes a threat, through the strain it imposes upon the heart and the blood vessels, exhibits not only an elevation of the systolic but also a distinct increase in the diastolic pressure. An hypertensive state is considered severe when the diastolic pressure reaches a level of 130; 140 is of common occurrence; values as high as 200, or more, sometimes develop.

True hypertensive states, that is those in which both systolic and diastolic pressures are very much elevated, present themselves in three forms to the clinicians:

1. Hypertension accompanying albuminuria.
2. Hypertension as a sequel to renal dysfunction.
3. Idiopathic (essential) hypertension.

Hypertension as an accompaniment of albuminuria was first recognized by Bright[21] in 1836, when in his series of "Cases of renal disease accompanied with the secretion of albuminous urine", he observed thirty-four cases of cardiac hypertrophy without any valvular disease. The hypertension associated with acute nephritis is well known; it is usually of short duration and is outside the present topic. Herrick and Tillman[22] found that a small but appreciable number of toxemias of pregnancy, when followed up, developed hypertensive disease after an initial albuminuric nephritis. The observation over a number of years of cases which began as albuminuria, in men as well as in women, has led me to the conclusion that hypertension frequently becomes the dominant complication of albuminuria and outstrips renal insufficiency, anemia or uremia as a cause of death. It may be that with the recent advances in the treatment of albuminuria, these patients live long enough to develop hypertension instead of succumbing to infections, as was so common a decade ago.

Hypertension as a sequel to renal dysfunction may be discussed under the headings:

1. Influence of hypertension on renal function.
2. Influence of diminished renal function on blood pressure.
3. Influence of renal ischemia on blood pressure.

The theory that hypertension was a compensatory process to enhance the action of the kidneys was first formulated by Traube[23] in 1876 and subsequently endorsed by Cohnheim[24] in 1880. Recently, in 1934, Page[25] showed that neither a spontaneous nor an induced fall of blood pressure affected renal function as measured by the urea clearance test. This evidence which bears out many clinical observations, sets aside the compensatory theory of the cause of hypertension. The level to which the blood pressure may be depressed without interfering with kidney activity of course has its limits. Lassen and Husfeldt[26] found when the systolic blood pressure had been lowered to well below 100 by means of spinal anesthesia, that the urinary flow was diminished. Such degrees of hypotension (the diastolic pressure presumably being fifty mm. of mercury or less) fail to deliver a glomerular capillary pressure of thirty or more to overcome the plasma colloid osmotic pressure of about thirty, a pressure which Richards[27] and his co-workers have found necessary for urine formation.

The demonstration that destruction or removal of the greater part of the kidneys is followed by an elevation of blood pressure, was first accomplished by Pässler and Heineke[28] in 1905. Janeway[29] in 1913 showed that after reduction of the dog's kidney substance there was a rise not only of the systolic pressure, but of the diastolic as well. Subsequent experimental work has amply verified these observations.

The clinician knows that hypertension follows renal insufficiency, whatever its cause. This holds true whether deficient kidney activity is due to obstruction of the urinary tract, Bright's disease or other renal involvement, such as polycystic degeneration of the kidneys. The proof of the causal relationship between hypertension and impaired kidney function is found in the fact that when obstruction of the urinary tract (whether it is due to new growth, stricture, stone or prostatic hypertrophy) is relieved, the blood pressure returns to a normal level. Frequently, hypertension does not develop with inadequate renal function, or drops while kidney activity is still diminished. The lack of blood pressure elevation under such circumstances is attributed to con-

stitutional weakness which lessens the power of the cardiac and arterial muscles.

Ischemia of the kidney, produced experimentally by constriction of the renal artery, results in a rise of blood pressure. This is a noteworthy contribution by Goldblatt;[30] its exact clinical application is not yet clear though without doubt it will prove to be important.

Essential–idiopathic–Hypertension. Essential hypertension may be defined as a functional disorder, characterized by a *progressively increasing* elevation of *both systolic and diastolic* arterial pressure; the mechanical strain incidental to the hypertension often produces changes in the heart and the arteries, especially those of the heart, the brain and the kidneys, so severe that death results.

Recognition of the independence of blood pressure from kidney disease in a certain group of cases, dates from a period after the invention of the first clinical instrument for measuring blood pressure by von Basch in 1876, and was formulated in terms that explained the trend of thought at that time:

"Latent arteriosclerosis"–von Basch

"Pre-sclerosis"

"Pre-albuminuric stage of Bright's disease"–Mahomed

"Hyperpiesis"–Clifford Allbutt

"Hypertensive cardiovascular disease"–Janeway

"Essential hypertension"

"Malignant hypertension"–Keith, Wagener and Kernohan

All these terms indicate that various clinicians have demonstrated to their satisfaction for many years that high blood pressure may occur independently of any affection of the kidneys. This is not recognized in all quarters today. Such doubt of the frequent independence of hypertension and kidney disease still rests very largely on the impressions of clinicians and pathologists antedating the perfection of renal function tests.

Any one who has studied cases of elevated arterial pressure during the last twenty years, knows that the patients with hypertension and without demonstrable lesions of the kidney or impairment of renal function, are numerous. A careful analysis of mortality statistics shows that the majority of deaths of persons between forty and sixty-five years of age, that is, individuals who die before they have lived their natural life span, is due to the sequelae of hypertensive disease.

The capillary pressure remains normal in hypertensive subjects, showing that the peripheral resistance is adjusted so that a normal capillary circulation is maintained. This was first demonstrated by Boas and Frant[31] in 1922 and since then has been verified many times. The question arises whether the peripheral resistance is primary and the hypertension a compensatory phenomenon, or whether the hypertension in the arteries initiates the vicious circle and is regulated by the arterioles at the distal end of the arterial tree.

The generally accepted view is that a generalized contraction of the arterioles causes hypertension. The idea that increased tonicity of the muscular arteries may bring about an elevation of the blood pressure and that the arterioles act as regulators which control the flow of blood to the capillaries, has been ignored and never refuted though it has been stressed by Pal[32] and others.

There is a good deal of evidence that the arterioles contract and dilate according to the local requirements of the tissues which they supply with blood. The observations of Krogh,[33] Richards,[27] and Cobb and Talbott[34] have shown that during quiescence only a fraction (in the kidneys 5 per cent) of the capillaries are patent in the voluntary muscles, kidneys, brain and presumably all tissues, while during periods of activity, all the available capillaries are open and filled with blood. It seems rather forced in view of these facts, to think of a generalized, fixed, peripheral resistance as existing throughout the body, since it is clear that the intermittent blood supply is adjusted by constant openings, contractions and closures of the arterioles which do not occur simultaneously throughout the whole body but are brought into play according to the needs of the individual tissues.

Two recent observations establish the fact that arterioles dilate or contract in response to a drop or increase in blood pressure. Page and Heuer[35] found that after section of dorsal and lumbar anterior nerve roots a drop in arterial pressure was accompanied by relaxation of spasm in the arterioles of the retinae though they were outside of the operative field, that could influence the retinal vessels directly. Flexner[36] studied the peripheral circulation in a case of coarctation of the aorta and demonstrated that the action of the arterioles was about the same in the arms where hypertension had resulted from aortic narrowing, as in the legs where the blood pressure was at a normal level.

All these points are arguments for the idea that increased arteriolar

or peripheral resistance is a compensatory phenomenon for a hypertension produced by other agencies presumably an augmented tonicity of the muscular arteries.

Malignant Hypertension

Volhard and Fahr[37] in 1914 coined the term "malignant hypertension" for those cases in which a high blood pressure was complicated by renal insufficiency. The name was abandoned until Keith, Wagener and Kernohan revived it and stressed neuroretinitis and hypertensive encephalopathy as the significant complications. Since then malignant hypertension has been defined in a great variety of ways, very few of which accord with one another. The malignant nephrosclerosis, first described by Fahr,[38] has been recognized and this designation has a justifiable background. Instead of thinking of essential hypertension as benign or malignant, it would serve a better purpose to classify this condition as mild or severe; the severe type including the cases with a diastolic pressure constantly above 140 or more, which constitutes a menace through various vascular complications. It is true that such hypertensive states often "manifest extreme malevolence" and in that sense are malignant but in clinical parlance the term malignant hypertension is associated with the complications of hypertension which, according to some, are not necessarily present, according to others, may be either retinal or renal or cerebral. There is no unanimity as to the exact symptom complex covered by the term malignant hypertension, and it would serve accuracy and simplicity if it were abandoned and replaced by more specific designations.

Summary

An attempt has been made to picture the clinical aspects of hypertension. Some of the facts suggested to the examining physician by a blood pressure reading have been analyzed. Many of the conclusions have not been orthodox but tinged by personal interpretation. However, this is justified since the physiology and functional pathology of blood pressure are not entirely clear, and the formulation of workable theories in regard to blood pressure are necessary for the physician so that underlying conditions may be diagnosed and purposeful treatment may be carried out.

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THE USE OF CONVALESCENT SCARLET FEVER AND MEASLES SERA IN PROPHYLAXIS AND THERAPY*

WILLIAM THALHIMER

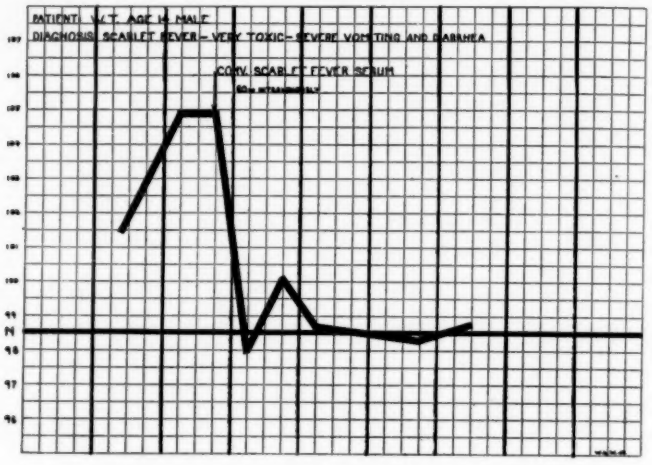
Manhattan Convalescent Serum Laboratory

It is well known that an attack of certain infectious diseases confers lasting, even lifelong immunity on the recovered individual. These individuals, known as immunes, can have intimate contact with these infectious diseases and still not contract them. This resistance results because the disease has caused the active and continuous development of immune substances in the tissues or blood, or both, of the recovered individuals. These substances neutralize the infectious agent when it attempts to gain entrance into the body, and, thereby, prevent infection.

This natural method of the development of immunity has been utilized in some diseases for the preparation, in animals, of serums for preventing or treating specific, infectious diseases. Diphtheria antitoxin is an example of one of these serums prepared by inoculating horses with the diphtheria toxin, which stimulates the development of antitoxin, just as the clinical disease diphtheria causes this effect in patients who recover. Diphtheria antitoxin, when injected under the skin of a child exposed to this disease is almost 100 per cent efficient in preventing the development of diphtheria. In this way diphtheria antitoxin developed actively in the horse is transferred passively to the exposed child. The resulting passive immunity is a temporary one which lasts for two to three weeks. Although of a temporary nature it is extremely important immediately to protect susceptible children from diphtheria, especially young children in whom the mortality is high. Diphtheria antitoxin, of course, also is very efficient therapeutically.

Weisbecker[1] in 1897 was the first one to find out that human serum obtained from an individual recently recovered from scarlet fever, when injected into another will cause a passive immunity, and also, will give excellent results with rapid cure in the treatment of patients in whom scarlet fever has already developed.

* Delivered February 18, 1938 in the Friday Afternoon Lectures Series.



This serum has been named convalescent serum since it is prepared from the blood of individuals who are convalescing from or have recently recovered from infectious diseases. A better name is "convalescents' serum".

My interest in convalescent serums was aroused six or seven years ago for several reasons.

First: Several convalescent serums have been proved, by a large experience, in many places, to have marked efficacy in prophylaxis or therapy, or both.

Second: Convalescent serums, which, of course, are human serums, are safe agents to use and practically never cause reactions, even when administered intravenously. These properly prepared human serums have been demonstrated to be as nearly bland material for intravenous administration as anything known to me. Febrile reactions, chills or serum sickness are extremely unusual, occurring in not more than ½ to 1 per cent of the instances, and have never, to my knowledge, caused concern or alarm to the attending physician. Sensitization and anaphylaxis, in my experience, are unknown. All this is in contradistinction to the risks from the injection of animal serums, even though animal serums have been much improved in this regard in recent years. In our experience, there are no reactions at all following the intramuscular injection of the properly prepared human serums, with the possible exception of a very occasional, mild serum sickness from seven

to ten days later, which has never required medication.

Third: The field for investigation is extremely large, and needs intensive work.

The serum is prepared according to the rigid regulations of the U. S. Public Health Service, and the laboratory, having satisfied these requirements, has received a federal license. Only Wassermann negative serums, which have been proved bacteriologically sterile, are used. These are pooled, usually in lots of thirty individual serums. Preservative is added, followed by Berkefeld filtration and bottling. Sterility tests are repeated on the bottled serum, and each pool is held at least seven days before being released by a negative sterility test.

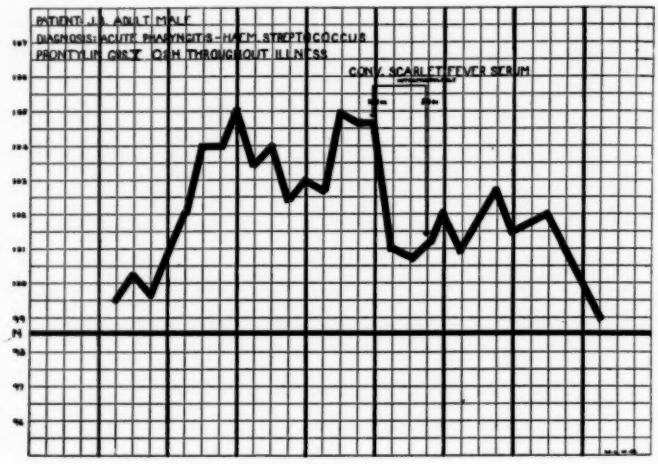
Extreme care and gentleness are used in handling the blood and serum, so as to prevent even a tinge of hemolysis, and bleedings are made only at least three hours after the donor's previous meal (so as to minimize the possibilitiy of food proteins being present in the serum).

It is my conviction that these precautions have eliminated reactions from the use of these human serums practically to the vanishing point. An experience of five years, covering thousands of injections of different types of convalescent serum administered by many physicians, both intravenously and intramuscularly, has demonstrated the practicability of preparing human serums which can be injected with no risk of severe reactions and with only the rare occurrence of a mild reaction.

Since all blood cells are removed by Berkefeld filtration, there is no possibility of agglutinable cells being present and causing a reaction. Also, whatever agglutinins the pooled serum contains, apparently are diluted sufficiently by the patient's entire circulating blood to prevent reactions. This also is the explanation of why blood transfused from universal donors into type II or III recipients has not caused reactions (except possibly in rare instances).

The serum has not caused sensitization, even when injections have been given to children at ten day intervals to prevent the reappearance of measles in a children's institution. With this procedure hospital wards can be kept open continuously even in the midst of epidemics.

Only adult donors are used, except in times of great prevalence of these two exanthemata (scarlet fever and measles), when children of fifteen or over may be used, after receiving the signed consent of the parents. Adults furnish 250 cc. of blood (by vein puncture) at each bleeding, for which they receive $5. This yields a net of about 100 cc.


PATIENT: J.B. ADULT MALE
DIAGNOSIS: ACUTE PHARYNGITIS-HAEM. STREPTOCOCCUS
PRONTYLIN GRS X O&M THROUGHOUT ILLNESS
CONV. SCARLET FEVER SERUM

of serum, after carrying out serological and sterility tests. The first bleeding can be made from recent convalescents after an afebrile period of seven days. Bleedings can be repeated in men at two week, and in women at three week intervals, without any deleterious effect and without any decrease in their hemoglobin percentage. Our data show that, on the contrary, the hemoglobin increases. It has been demonstrated that no significant fall in potency occurs in the serum secured from an individual for, at least, four months after onset in scarlet fever and measles. This period may be longer, and if investigation in progress demonstrates this, the source of supply will be correspondingly increased. Serum kept at four degrees centigrade retains its potency for at least a year.

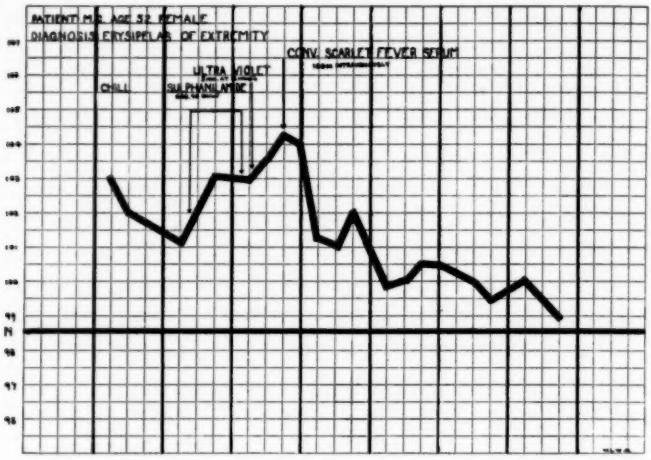
It might be well to discuss measles convalescent serum first.

Undoubtedly you will be interested to know that in 1916 Dr. William H. Park (with Zingher's cooperation) was the first in this country to employ convalescent serum for the prevention or attenuation of measles. This work was carried out independently, the same year as that of Nicolle and Conseil,[2] who published their results in 1918, Dr. Park not publishing until 1924.[3,4,5] Since these publications, more or less sporadic studies have been made in many places but only in recent years have centers been organized in a few European and American cities making enough convalescent serum available for extensive use. All of these trials, both small and large, have demonstrated the marked effi-

ciency of this method of measles prevention or attenuation.

Measles is usually considered a mild disease, inconvenient but inevitable. Therefore, it might be surprising to learn that in infants up to one year of age, who contract measles, the mortality rate is 8 per cent, in the one to two year age group 5 per cent and in those from two to three years old 1.5 per cent. These fatalities are caused mainly by the not uncommon serious complications of measles, such as pneumonia and mastoiditis. But from ten years of age on the mortality rate is much less, yet not insignificant, i.e., 0.1 per cent to 0.2 per cent. Stated in another way, 95 per cent of all deaths from measles occur in children four years old and under. Accordingly, the older a child is when accidentally infected with measles, the less likely he is to suffer serious complications or death. One further illustration, quoted from Godfrey,[6] is very illuminating. In New York State, from 1915-1924 there were 35,930 cases of measles reported among children under three years of age, in places of less than 200,000 population. Of these, 1,441 died, a fatality rate of 4 per cent. Had these attacks of measles been postponed until the children were between five and fourteen years old, only fifty-four would have died and the lives of 1,387 children in this group would have been saved. In other words, if there were a method which did no more than allow one to postpone measles until after children reached their fifth year, many lives could be saved. Apparently, it is not generally known that such a method does exist. If used within five days after exposure, it can prevent the disease in up to 95 per cent of those exposed, thereby postponing the contraction of measles till the children are older and in a more resistant age group when again accidentally exposed. The method has the further advantage, that if used within one week after exposure it can modify the infection to a mild, attenuated measles, practically sure to be free from serious complications. This attenuated measles is often so mild that it is difficult to diagnose, and yet the attenuated attack apparently confers sufficient permanent active immunity to prevent the disease occurring again.

It has been shown that the maximum percentage of prevention is achieved only if the serum is injected intramuscularly within five days after exposure. The minimum dose for children five years old or less is 5 cubic centimeters and for older children one cubic centimeter for every year of their age. Prevention can then be expected in from 70 per cent to 95 per cent of the injected children. Even in those instances



where complete prevention does not occur, a modified and attenuated attack will occur in all but 3 per cent to 5 per cent of the total group. One can readily see the advantage of limiting measles in healthy children to this mild disease with its subsequent immunity. As a matter of fact, attenuation should be the method of choice except in debilitated or sick children, in children five years of age or less, and in children exposed accidentally in hospitals and institutions. The reason for attempting complete protection in all children not over five years old, even though they are robust and in good health, is that the mortality from measles is confined mainly to this lower age group.

The full dose of serum has some chance of preventing the disease even if administered between the fifth and seventh day after exposure, and even if it fails to prevent the disease, usually causes attenuation. On and after the eighth day of exposure very little protection can be expected.

For attenuation, which is advised as the method of choice in healthy children over five years of age, one-half of the usual dose of serum should be injected not later than the fifth day of exposure, or the full dose from the sixth to the seventh day.

It also is well known that pooled normal adult serum is as efficient in the prophylaxis of measles as the specific convalescent serum, but it must be used in four times the amount, and normal whole blood in about eight times the quantity.[7,8] The disadvantage, formerly, in using normal

serum was the larger amount which had to be injected.

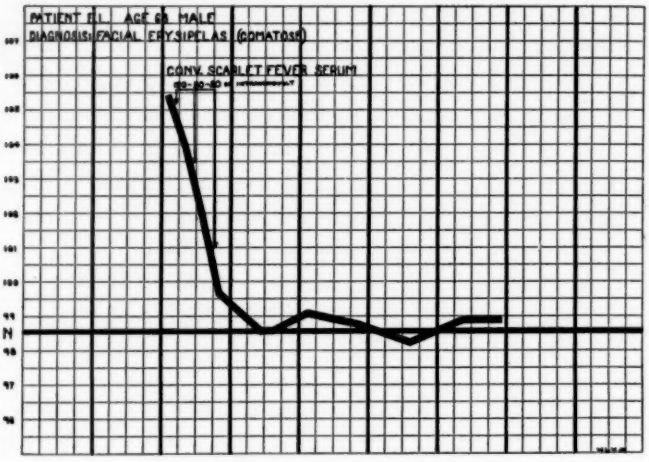
However, now we have several methods available for concentrating serum, and, thereby, reducing the amount of immune measles serum to be injected to the same volume needed when convalescent serum itself is injected. One method, which was developed recently in our laboratory, is by concentrating the serum in sterile, viscose casings; another is by precipitating the globulin of the serum, which was investigated by Dr. Samuel Karelitz[9,10,11] with the cooperation of Dr. K. G. Falk and Mr. C. Greenwald of the Research Laboratory of the Department of Health in the preparation of the globulin fraction. There, also, are several methods of freezing and drying serum, and redissolving it in a small amount of sterile distilled water.

There is no other method of preventing measles except with material obtained from human blood or similar sources (placental globulin,[12,13] with which I have had no experience).

In 1914, again it was Dr. Park who carried out the first work in this country with convalescent scarlet fever serum. This work was done under his direction by Zingher.[14,15]

Many reports since, in many countries, have shown the marked therapeutic value of pooled convalescent scarlet fever serum when this is given in large enough amounts and especially when administered intravenously early in the disease. The beneficial results have been so definite that in many articles recommendations are made for the organization of agencies for collecting and distributing convalescent serum. Blood, yielding potent serum, can be drawn on the twentieth day after the onset of illness, provided the patient is convalescing and has been fever free for at least seven days; and further bleedings may be made at two or three week intervals for a period of four months from the onset of the illness. About eight years ago, with the cooperation of the Chicago Department of Health and of a number of colleagues, and with a grant of funds, it was possible for me to organize the Samuel Deutsch Convalescent Serum Center at Michael Reese Hospital, and similarly, three years ago the Milwaukee Convalescent Serum Center at Columbia Hospital, Milwaukee. Some of the observations in Chicago have been published with Hoyne and Levinson.[16]

Eight hundred and seventy-two children, giving no previous history of scarlet fever, and unavoidably exposed in their homes to this disease, were passively immunized with from 10 to 20 cc. of pooled convalescent



serum, and only 2 per cent developed mild scarlet fever and 1 per cent genuine scarlet fever. In similarly exposed home contacts, Park states that in his experience about 10 per cent contract scarlet fever; and Gordon's findings in Detroit were 15 per cent. From 90 to 93 per cent were protected who were expected to contract the disease.

The doses for prophylaxis which we are recommending and which seem to be giving excellent results are 10 cc. by intramuscular injection to children up to five years of age, 15 cc. to those whose age is from five to ten years and 20 cc. for older children.

The results of therapy have been published of 947 severely ill hospitalized patients and 983 home treated patients of varying degrees of severity, 1,930 patients in all. The hospitalized patients were treated in the Chicago Municipal Contagious Disease Hospital under the direction of Dr. Hoyne.[16] Only severely sick patients received serum, usually on admission, and 6,282 mildly or moderately ill patients, admitted to the hospital during the same period, treated symptomatically and not receiving serum, served as controls.

Some of the findings can be briefly re-stated. Patients without septic complications showed an average fall of temperature of two and a half degrees in the first twenty-four hours and a total of three degrees in the first forty-eight hours when they received the convalescent serum within the first three days of their illness.

Not infrequently the disease was rapidly aborted, and even a toxic

patient with a temperature of 104-105 degrees was converted in twelve hours into a convalescent patient, with normal temperature, followed by an uninterrupted rapid convalescence.

When the serum was given from the fourth to sixth days of the disease the temperature drop was from one-half to one degree less. With the decline of temperature in the patients treated early, there was a corresponding and marked diminution of toxicity, fading or disappearance of the rash, relief from angina, nausea and vomiting, return of appetite, and shortening of the period of illness. Most patients with complications on admission or mildly ill but later developing complications were also greatly benefited by serum.

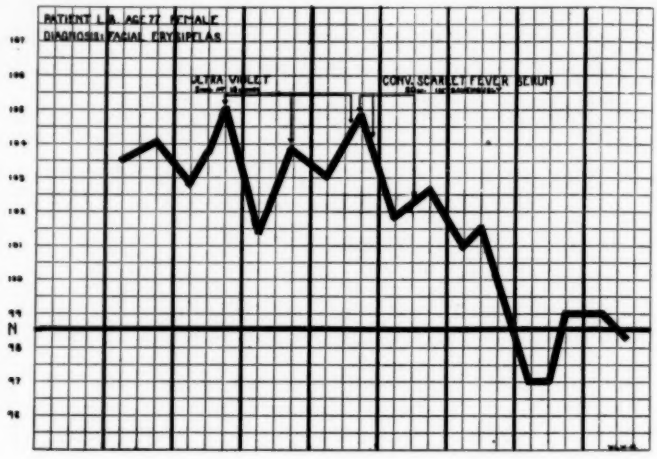
The evidence definitely shows also that severely ill, serum treated individuals developed a smaller number of less severe complications than the mildly or moderately ill in the control group not receiving serum.

The dosage, depending on the size of the individual and the severity of the illness, varied from 20 to 100 cc. It was administered intravenously and occasionally had to be repeated.

The value of intravenous administration over the intramuscular method cannot be over-emphasized. When the serum is injected into the vein it is distributed immediately throughout the entire blood stream and entire body. Hence, therapeutic action begins immediately. However, it takes from fourteen to sixteen hours for maximum absorption to occur after intramuscular administration, and even then the potency of the serum in the blood is only one-half of what it would have been had the same dose been given into the vein. It is the safety with which one can administer human serum that allows us to recommend the intravenous method rather than any other.

It is well recognized that a specific, therapeutic serum must be administered early in the course of an infectious disease, in order to secure maximum curative results. This holds just as true with the early administration of convalescent scarlet fever serum as with any other serum, such as diphtheria antitoxin. If one is to use convalescent scarlet fever serum therapeutically in severely ill scarlet fever patients, this serum should be administered in proper doses intravenously as soon as the diagnosis is made.

Another important use of convalescent scarlet fever serum is in the treatment of various types of hemolytic streptococcal infections



other than those arising from scarlet fever.[17] The reason for this, apparently, is that virulent, hemolytic streptococci causing various types of infection are closely related to those occurring in scarlet fever. They give rise to similar toxins which are neutralized by similar antitoxins.

Since the convalescent serum laboratory has been opened in New York, many physicians have used convalescent scarlet fever serum, on our advice, in the treatment of a large number of patients with severe streptococcal infections of the limbs, with streptococcal pneumonia, with severe forms of erysipelas, with streptococcal blood stream infections, and other serious types of streptococcal infections. All of these patients have been desperately ill, and the lives of many have been despaired of, even after all other types of treatment have been used. Many of these patients have made rapid recovery. Considering the desperate plight of these patients the physicians have considered many of these results to be quite startling. A statistical analysis of these results is impossible, because it is impossible to secure a control group of similar patients. Once a therapeutic agent is known to be of value it cannot be denied to anyone, and, therefore, the observation of a control, untreated group is impossible. One can estimate the significance of the results on the basis of previous experience.

Recently a very remarkable drug, sulphanilamide, has been extensively used in the treatment not only of streptococcal infections, for which it was introduced originally, but for other types of infection as

well. Many of the results with sulphanilamide treatment have been remarkable, but peculiarly enough it has been found by a number of observers to cause very little or no benefit in the treatment of scarlet fever.[18] It has been found, also, that sulphanilamide, at times, causes toxic effects and may even cause disaster; therefore, this potent drug must be used with care and at times must be discontinued. Some of the results referred to above in the treatment of patients desperately ill with various types of streptococcal infections have been achieved when sulphanilamide failed or when sulphanilamide had to be discontinued.

It should be emphasized again that convalescent serum is as nearly bland and innocuous a material as we know of, and, when properly prepared, in our experience has never produced any bad effects, which caused concern to the attending physicians. Whereas the exact method of action of sulphanilamide is not known, some experimental work by Rosenthal[19,20] indicates that a specific, therapeutic serum may complement the action of sulphanilamide, so that these two substances act synergistically. This means that when given together the beneficial effect is greater than the summation of the effect of each given separately. Therefore, during the past year since sulphanilamide has been available, some patients have received both of these agents simultaneously with excellent results.

It has been found that convalescent scarlet fever serum is an excellent material for producing the Schultz-Charlton blanching phenomenon, which, at times, is an important aid in the diagnosis of a scarlet fever rash. One cubic centimeter of this serum should be injected intracutaneously, and this small amount of serum, put up in ampoules, can be obtained at our laboratory. Again the use of human serum for this test avoids the use of animal serum with the possibility of reactions, sensitization, etc.

The Manhattan Convalescent Serum Laboratory is located in the Research Laboratory of the City Department of Health, on the same grounds where Dr. Park years ago did the first work in this field in this country. It is a non-profit organization, and its work has been made possible by the grant of funds from the Nathan Hofheimer, New York and Friedsam Foundations, and the Lederle Laboratories.

In order to maintain a supply of serum it is necessary to charge the cost of production of these serums. Until now the laboratory has not become self-supporting, but it is hoped that it will become so in the

future.

The demand for serum by physicians and hospitals has become so great that it is only with the greatest difficulty that we have been able to secure a sufficient supply to satisfy these demands. We need the help of all physicians in our endeavors to secure a sufficient amount of convalescent serum. Physicians can be of the greatest service in advising their private adult and adolescent patients immediately after recovery from measles or scarlet fever to cooperate with the Manhattan Convalescent Serum Laboratory. Only 250 cc. of blood are taken at a time, and for this each donor is paid $5 immediately. In our experience with many thousands of donors this has never caused the donor any harm. Since we take special care to make this a painless procedure with a small intracutaneous injection of novocain, the donors willingly return at three-week intervals for a period of four months to do their share in furnishing serum to aid others, especially children, exposed to or suffering from the disease from which the donors have just recovered. Physicians, also, have been extremely cooperative in advising their patients to help in this work.

The laboratory appreciates the help that has been given by many physicians, and will endeavor to maintain its effort to cooperate with physicians and hospitals in the control and treatment of infectious diseases.

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ANNOUNCEMENT OF EDWARD N. GIBBS MEMORIAL PRIZE

IT IS announced by The New York Academy of Medicine, 2 East 103 Street, New York City, that a sum of approximately $1,000 is available under the Edward N. Gibbs Memorial Prize toward original research in Diseases of the Kidney during 1938.

Candidates, who must be physicians who have been graduated at least three years and be residents of the United States, shall submit "evidence of research already performed and of facilities to prosecute research upon the causation, pathology and new methods of treatment of diseases of the kidney".

The award may be continued through not more than three years to any one individual.

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PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

MAY 5—*The New York Academy of Medicine.* Executive Session—a] Reading of the minutes; b] Presentation of diplomas ¶ Joint meeting of The New York Academy of Medicine and the Welfare Council of New York City; Presiding: James Alexander Miller, president, The New York Academy of Medicine—a] Chronic illness in New York City: Findings of the National Health Survey, G. St. J. Perrott, principal statistician, National Health Survey of the United States Public Health Service; b] A community program for the care of the chronically ill: Based upon the hospital survey for New York, Ernst P. Boas, chairman, Committee on Chronic Illness of the Welfare Council of New York City. ¶ Report on election of members.

MAY 19—*The Harvey Society (in affiliation with The New York Academy of Medicine).* The eighth Harvey Lecture, Experimental Hypertension Induced by Renal Ischemia, Harry Goldblatt, Professor of Experimental Pathology, Western Reserve University.

SECTION MEETINGS

MAY 3—*Dermatology and Syphilology.* Executive Session—a] Reading of the minutes; b] Election of section officers and member of Advisory Committee — For chairman, Eugene F. Traub, for secretary, Louis Tulipan, for member of Advisory Committee, Max Scheer. ¶ Presentation of cases—a] New York Polyclinic Hospital; b] Beth Israel Hospital; c] Good Samaritan Dispensary; d] Sea View Hospital; e] Miscellaneous cases. ¶ Discussion of selected cases.

MAY 6—*Surgery.* Executive Session—a] Reading of the minutes; b] Election of section officers and member of Advisory Committee—For chairman, Frank L. Meleney, for secretary, J. William Hinton, for member of Advisory Committee, Roderick V. Grace. ¶ Presentation of cases. ¶ Papers of the evening—a] After treatment of Colles' fracture, Frederick Henry Amendola; Discussion by Condict W. Cutler; b] Problems in treatment of fractures in children, Fenwick Beekman, John E. Sullivan; c] Preliminary report on a new pin method for treatment of fractures of shafts of the long bones, Kenneth M. Lewis, Lester Breidenbach; d] Open reduction and fixation as a primary procedure in adult fractures of the long bones, Clay Ray Murray; Discussion by William Darrach. ¶ General discussion.

MAY 10—*Joint Meeting, Neurology and Psychiatry and the New York Neurological Society.* Executive Session, Section of Neurology and Psychiatry—a] Reading of the minutes; b] Election of section officers and members of Advisory Committee—For chairman, Morris Grossman, for secretary, Lewis Stevenson, for two members of Advisory Committee, George H. Hyslop, for two years to fill unexpired term of James H. Huddleson, resigned; Irving H. Pardee, for five years. ¶ Papers of the evening—a] On the topography of a probable sleep-regulating center, Joseph H. Globus, Discussion by Henry A. Riley; b] The treatment of neurogenic megacolon by selective drugs, Walter O. Klingman; Discussion by Edward J. Donovan, Angus M. Frantz, Henry A. Riley; c] Psychopathological aspects of emotional divorce, Philip R. Lehrman; Discussion by Clarence P. Oberndorf, Louis Casamajor, Irving Pardee, Israel Wechsler, S. Bernard Wortis, George Hyslop, Simon Rothenberg (by invitation). ¶ General discussion.

MAY 11—*Historical and Cultural Medicine.* Executive Session—a] Reading of the minutes; b] Election of section officers and member of the Advisory Committee —For chairman, Howard Reid Craig, for secretary, Louis Casamajor, for member of the Advisory Committee, Reginald Burbank. ¶ Papers of the evening—a] Medieval origins of the modern hospital (lantern slides), Edward F. Hartung; b] Konrad Gesner—scholar physician (lantern slides), Thomas P. Fleming (by invitation). ¶ General discussion.

MAY 12—*Pediatrics.* Case Demonstrations. ¶ Executive Session—Election of section officers and member of Advisory Committee—For chairman, Philip M. Stimson, for secretary, Lucy Porter Sutton, for member of Advisory Committee, Samuel Z. Levine. ¶ Presentation of single case reports—a] Israel Zion Hospital — Esophageal varices and thrombosis of the splenic vein, H. M. Greenwald; b] New Rochelle Hospital—Hemorrhagic disease of the new born, Fairfax Hall; c] Babies' Hospital—Dermatomyositis, Ralph V. Platou (by invitation); d] Mount Sinai Hospital—Lipoid granulomytosis, Howard G. Rapaport (by invitation); e] New York Infirmary for Women and Children—Unusual carbohydrate metabolism, Marion Josephi (by invitation); f] New York Hospital —Dermatorrhexis (Ehlers-Danlos syndrome), Carl H. Smith; g] Roosevelt Hospital—Post-infectious cervical subluxation, Alexander T. Martin, M. Becket Howorth; h] Willard Parker Hospital — Mastoiditis in scarlet fever with ligation of the common carotid artery, Francis W. White; i] St. Luke's Hospital—Injury of child by roentgen rays during pregnancy, F. Elmer Johnson; j] Post-Graduate Hospital—A variety of spotted fever, Irving Posner (by invitation); k] Metropolitan Hospital—Tuberculous meningitis resembling diabetic coma, Louis L. Krafchik (by invitation); l] Lenox Hill Hospital—Gangrenous cholecystitis with perforation, Irwin P. Sobel, Discussion by J. Leopold; m] Knickerbocker Hospital—Intussusception with presentation of appendix at anus, Irving LeBell (by invitation); n] Harlem Hospital—Congenital obliteration of the bile duct, Reuben Steinholz (by invitation); o] Flower-Fifth Avenue Hospital—Osteopetrosis (Albers-Schönberg's disease), Forris E. Chick (by invitation), Discussion by M. Bass; p] Bronx Hospital—Icterus gravis, Henry M. Weismann (by invitation), I. Rothstein (by invitation).

MAY 16—*Ophthalmology.* Examination of cases (bring instruments). ¶ Executive Session — a] Reading of the minutes (8:15); b] Election of section officers and member of Advisory Committee—For chairman, James W. White, for secretary, Rudolf Aebli, for member of Advisory Committee, Martin Cohen. ¶ Paper of the evening—The intraocular tension in sarcoma of the choroid and ciliary body, John H. Dunnington. ¶ Case reports—a] Trauma with secondary orbital infection and retinal changes; b] Lymphoma or Mikulicz's disease of the lacrimal glands; c] Hypertelorism (this case shows wide-spread orbits and distinctive x-ray findings), Webb W. Weeks; d] Anomalous retinal vein crossing the macula, A. L. Kornzweig (by invitation); e] Precancerous melanosis of the lids and conjunctiva, Algernon B. Reese; f] Disappearance of the iris after prolonged hyphemia; g] Fistula of the lacrimal gland, Guernsey Frey; h] Sudden dislocation of the lens in the anterior chamber, of congenital origin in two members of a family, followed by secondary glaucoma; Extraction of lenses; i] Unilateral exophthalmos due to a sclerosing sarcoma of the anterior middle cranial fossae, Martin Cohen; j] Tay-Sachs disease, Joseph Laval; k] Zonular opacity of the cornea, M. Davidson; l] Retrobulbar neuritis with partial closure of the central retinal artery, Walter F. Duggan (by invitation); m] Retinitis punctata albescens; n] Keratitis neuroparalytica, Morris Jaffe (by

invitation); o] Dacryoadenitis, Henry Minsky; p] Superficial punctate keratitis in a young boy; q] An interesting fundus lesion; r] Ankyloblepharon with heterachromia of the iris, R. Townley Paton, McClelland Shellman (by invitation); s] Occupational kerato-conjunctivitis in a brass worker, Frances Richman (by invitation); t] Von Hippel's disease (angiomatosis retinae), Benjamin C. Rosenthal (by invitation); u] Retinitis pigmentosa. Hole in macula of one eye; v] Bilateral glaucoma controlled by a LaGrange iridectomy, Charles A. Perera (by invitation); w] Photographic studies of a case of intraocular foreign body before and after removal, Donald W. Bogart (by invitation); x] An operation for congenital ptosis, Giralamo Bonaccolto; y] Proptosis in a six weeks old infant, Morris Greenberg.

MAY 17—*Medicine.* Executive Session—Election of section officers and member of Advisory Committee — For chairman, Thomas T. Mackie, for secretary, Samuel W. Lambert, Jr., for member of Advisory Committee, Joseph Hajek. ¶ Papers of the evening—a] The diagnosis and treatment of gonorrheal endocarditis, John S. Davis, Jr.; Discussion by Ralph H. Boots; b] Oil aspiration pneumonia and pneumolipoidosis, Philip G. C. Bishop; Discussion by H. Pinkerton, Boston (by invitation); c] The therapeutic aspects of gastric and duodenal ulcer with hemorrhage, Burrill B. Crohn, Henry H. Lerner (by invitation); Discussion by William H. Glafke.

Genito-Urinary Surgery. No meeting of the section of Genito-Urinary Surgery was held in May. ¶ The following section officers and member of the Advisory Committee were elected at the meeting of the section held April 20: Chairman, John A. Taylor, secretary, Simon A. Beisler, member of Advisory Committee, Roy B. Henline.

MAY 18—*Otolaryngology.* Executive session —a] Reading of the minutes; b] Election of section officers and member of Advisory Committee — For chairman, Francis W. White, for secretary, Fred W. Graef, for member of Advisory Committee, John D. Kernan. ¶ Paper of the evening—Affections of the cricopharyngeal fold, Mr. Victor E. Negus, London, England (by invitation); Discussion by John D. Kernan, Charles J. Imperatori. ¶ General discussion.

MAY 20 — *Orthopedic Surgery.* Executive session—a] Reading of the minutes; b] Election of section officers and member of Advisory Committee—For chairman, Joseph B. L'Episcopo, for secretary, David M. Bosworth, for member of the Advisory Committee, Earl E. VanDerwerker. ¶ Papers of the evening —a] Athletic injuries, Marvin A. Stevens (by invitation); b] Analysis of three hundred and thirty cases of supracondylar fractures from the Children's Surgical Service of Bellevue Hospital, Irwin E. Siris; c] Hoke arthrodesis for flaccid flat feet in children, Peter E. Sabatelle (by invitation); d] Demonstration of motor bone unit, S. Lloyd Fisher (by invitation); ¶ Discussion.

MAY 24—*Obstetrics and Gynecology.* Executive session—a] Reading of the minutes; b] Election of section officers and member of Advisory Committee—For chairman, Edward H. Dennen, for secretary, Alfred M. Hellman, for member of Advisory Committee, Louis J. Ladin. ¶ Papers of the evening—a] Autopsy findings in still-births and neonatal deaths: a report of 200 cases, John W. Hammond; Discussion by Anthony Rottino (by invitation); b] A critical analysis of blood loss following delivery, with special reference to the value of ergotrate, Arthur M. Reich; Discussion by Harvey B. Matthews, John B. Pastore (by invitation); c] Further observations on the endocrine basis of toxemia of pregnancy, with a classification of hypertension in pregnancy, Jefferson J. Vorzimer (by invitation); Discussion by William Herrick, Raphael Kurzrok.

AFFILIATED SOCIETIES

MAY 16—*The New York Roentgen Society (in affiliation with The New York Academy of Medicine).* Interesting cases. ¶ Paper of the evening—X-ray diagnosis of functional foot disorders, Dudley J. Morton (by invitation); Discussion opened by T. Campbell Thompson (by invitation) Maurice M. Pomerantz. ¶ Executive session—Annual meeting and election of officers.

MAY 18—*New York Section of the Society for Experimental Biology and Medicine* Variations in pathways by which equine encephalomyelitis viruses invade the CNS of mice and guinea-pigs, Albert B. Sabin, Peter K. Olitsky. ¶ Age of host and capacity of equine encephalomyelitis viruses to invade the CNS, Albert B. Sabin, Peter K. Olitsky. ¶ Effect of age of the host on resistance to tuberculous infection, K. C. Smithburn. ¶ Effects on blood pressure of injections of urine extracts of normal and hypertensive individuals, J. H. Leathem (Introduced by W. W. Swingle). ¶ The unidentified base in gelatin, Donald D. Van Slyke, Alma Hiller (by invitation), Robert T. Dillon (by invitation), Douglas MacFayden (by invitation). ¶ Transmission of mouse sarcoma with small numbers of counted cells, Morton C. Kahn, Jacob Furth. ¶ "Acid" phosphatase activity of the serum of normal human subjects, Alexander B. Gutman, Ethel Benedict Gutman (by invitation). ¶ Business session.

MAY 26—*New York Pathological Society (in affiliation with The New York Academy of Medicine).* Papers of the evening —a] Classification of the pathology of infected abortions, Henry C. Falk (by invitation); b] Experimental studies of tissue reactions to lipids the formation of acid-fast membranes around certain oils and waxes, Irving Graef, William Kaufmann (by invitation), Leo Kaplan (by invitation); c] Disseminated lupus erythematosus in a male with some unusual findings, Arthur Ginzler (by invitation), T. T. Fox (by invitation). ¶ Executive session.

MEMBERS ELECTED

APRIL 8, 1938

MEMBERS

Max Bernanke, 239 Central Park West
Louis Berk, 215 East 73 Street
Edwin B. Bilchick, 876 Park Avenue
John G. Copeland, 24 Dove St., Albany
Caldwell B. Esselstyn, 16 East 90 Street
Donald Malven
7 Adriance Ave., Poughkeepsie
Frank Ober, 234 Marlborough St., Boston
Gerald H. Pratt, 219 West 44 Street
Jeremiah T. Simonson
365 West End Avenue
Thomas J. White, 221 Union St., Jersey City

MAY 5, 1938

William Travis Gibb, Jr., 140 East 54 Street
William H. Resnik
65 South St., Stamford, Conn.
Samuel B. Schenck, 876 Park Avenue

ASSOCIATES

Franklin Hollander, 203 West 81 Street
William C. MacTavish
142 Edgemont Rd., Scarsdale, N. Y.